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9th PAN ARAB CANCER CONGRESS

7 - 9 May 2009 - Cairo, Egypt
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AMAAC Introduction

The Arab Medical Association Against Cancer (AMAAC) is a medical body that was established in 2001 as part of the Arab Medical Association where its main office is located in Cairo - Egypt, and it is also a continuation of the Arab Council Against Cancer that was founded in 1995. The Executive Committee of (AMAAC) is represented by two members who are named officially by the Oncology Society of each Arab Country.

The Arab Medical Association Against Cancer aims at strengthening relationships between members in different Arab Countries to raise the level of cooperation in the field of oncology on both scientific and practical aspects. Exchanging information and researches between members through Regional and Arab Conferences and Publications. Holding Public Awareness Campaigns in the field of oncology that are organized by Arab Countries. Participating in scientific activities with International Oncology Societies. Finally, encouraging researchers and doctors to meet and exchange experiences together with finding training opportunities in the field of oncology inside and outside the Arab World.

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Dear Colleagues,

We are happy that the current issue of the Pan Arab Journal of Oncology (PAJO) includes the Proceedings of the PACC 2009. Indeed, the PAJO is the official publication of the Arab Medical Association Against Cancer aiming to disseminate, promote and improve the level of scientific publications in the Arab World. The policy of the PAJO Editorial Board is to encourage publications from the region, policy endorsed by the distribution of the PAJO free of charge to around 2000 Oncologists and Healthcare professionals. In addition, issues of the PAJO are put on the website of the AMMAC (http://www.amaac.info/05.htm) as soon as published. PAJO is a peer-reviewed journal looking for the high quality of work and aiming to encourage the publications from our region. Thus, we would like to urge you to send us reports of your research activities, case reports, reviews, articles to us and we will be happy to submit them to our reviewers for positive and constructive feedback. Why should we publish? It is crucial for our improvement process to have publication emerging from our countries because publication equal knowledge, investigations and willingness to improve. Your efforts are fundamental and vital to PAJO helping it to be indexed in Medline and to get an Impact factor. Counting on your Commitment to contribute to the PAJO and looking forward to a successful PACC meeting…..

Marwan Ghosn, MD, MBA / MHM
The AMAAC proudly presents the 9th PACC 2009

Under the patronage of

H.E. Mrs. Suzan Mubarak

The First Lady of the Arab Republic of Egypt

Honorary Presidents

H.E. Hatem El Gabaly, MD Minister of Health & Population
Dr. Sherif Omar, MD Chairman of Education & Scientific Committee, Egyptian Parliament

Dear Colleagues,

Over the past 20 years, the Arab Medical Association Against Cancer (AMAAC) has been progressively growing to become the central body providing both educational and training support to all oncologists within the Arab countries.

This year, Cairo once again will host our 9th PACC Congress. We greatly acknowledge the genuine support of H.E. Mrs. Suzan Mubarak, the first lady, who does not only provide strength to our group, but also provides hope to all cancer patients in the Arab world.

The 2009 AMAAC will focus on «Translating Evidence to Practice» in an attempt to reach an accordance concerning optimization of cancer management in our countries.

Our scientific committee has invited a distinguished faculty from the most reputable cancer institutions around the world, in addition to a group of well known high caliber speakers from many cancer centers in the Arab countries.

We have much to celebrate this year, as the treatment of cancer has improved over the past 20 years offering more effective options for patients. Further more the application of screening programs in many Arab countries will give a real hope of reducing cancer mortality in the near future.

With your active participation through submission of abstracts and interactive discussion during the congress, we will be able to accelerate the process of cancer treatment and broaden the scope of cancer research in the Arab countries.

In the 2009 AMAAC congress, we aim to keep our promise of seeking excellence and increasing the level of satisfaction and interest of our participants and colleagues across the Arab world.

We also promise to give you enough time to enjoy the allure and beauty of Cairo.

See you in May.

Kind regards,

Sami Khatib, MD Congress President
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Breast Cancer in Arab Countries

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Breast cancer has become one of the most important health problems for women in many Arab countries. It is the most common cancer among women from many Arab countries. We will review all available data regarding incidence, stages at presentation, type of surgery, availability of radiotherapy, and efforts at early detection and prevention.

Cancer prevention and early detection are the most effective ways to control the disease. Early detection of breast cancer is considered part of prevention of the disease. Breast cancer is the most frequent cancer in Arab women constituting 14% to 42% of all women cancers. ASR Incidence Rates vary from 9.5 to 50 cases/100,000 women/year with recent reports rising even further. Breast cancer in Arab countries presents almost 10 years younger than that in USA and Europe. Median age at presentation is 48-52 yrs and 50% of cases are below the age of 50 whereas only 25% of cases in industrialized nations are below the age of 50 years 1. Age-adjusted incidence rates ASR for breast cancer has increased in many Arab countries such as Lebanon (from 20 in 1996 to 46.7 in 1998 and up to 69/100,000 women/year), Jordan (ASR was increased from 7.6/100,000 women in 1982 to 32.8/100000 in 1997), Palestinians (ASR up by 93%), Egypt ASR up to 49.6, Kuwait ASR up to 50 as well as other Arab Gulf countries. Although the rates are still below those in industrialized nations, they are rising and may be expected to reach the same levels. Rise may be due recent changes in lifestyle, a diet more rich in animal fat, decrease in physical activity and exercise, delay of ages of marriage and first pregnancy from the late teens and early twenties to later ages. Breast feeding has decreased. Other risk factors may include radiation exposure, pollution and exposure to carcinogenic compounds such as pesticides but remains unknown. Prolonged exposure to birth control pills in premenopausal women, and especially hormone replacement therapy in post-menopausal women increase the risk of breast cancer are not well documented in Arab countries. Reports on genetic mutations of high-risk low-prevalence genes BRCA-1, BRCA-2 are limited in Arab populations while reports on low-risk high-prevalence genes such as CHEK2 are non-existent. Late presentations are very common. 60%-80% of cases are locally advanced or metastatic. Delays are due lack of education, shyness and fear. Young women tend to have their diagnosis of breast cancer delayed because of decreased awareness and low index of suspicion from their primary physicians. Patients often wait till tumors have grown larger of became attached to the underlying chest wall, or the overlying skin. The patient may present with redness of the skin or ulceration. A bloody nipple discharge may be the presenting complaint. A palpable mass in the axilla is not an uncommon presentation in cases of locally advanced breast cancer. Inflammatory breast cancer presents with a rapidly growing inflamed, thickened and red overlying breast skin was thought for some time to be very common in Tunisia but recent reports indicate that inflammatory breast cancer represents only 5-7% of cases in Tunisia. However, recent widespread campaigns of awareness and efforts at screening, in several Arab countries have led to detection of cases at early stages such as small lumps or abnormal mammography findings and microcalcifications. The goal of prevention is to reduce the incidence of breast cancer and to reduce breast cancer associated mortality. Primary prevention refers to methods aiming to reduce incidence by eliminating causes and carcinogenesis through dietary changes, exercise, reducing obesity or surgery to BRCA carriers, or chemoprevention with tamoxifen or raloxifen, or more recently lasofoxifene; and by controlling and reducing the use of hormone replacement therapy in post-menopausal women. Reduction of Incidence and Mortality from breast cancer may be achieved by secondary prevention which refers to screening and early detection. Screening is designed to discover small tumors before they manifest themselves clinically. To achieve goals of screening and early detection, that is, reduce incidence and mortality, society should plan on discovering tumors at early stages and be able to treat them successfully. Improving quality of diagnosis and treatment is an essential part of a national plan to control breast cancer. Population Screening is rarely practiced in most Arab Countries. When it is done, where resources are available, it should include Breast Self Exam (BSE), Clinical Breast Exam (CBE) and annual Screening Mammography starting at age 40 1. Locally advanced cases could be easily seen and/or palpated. Advanced breast cancer is devastating not only to women, but also to husbands and children. Husbands should be targeted to encourage women to enroll in awareness, screening & early detection campaigns. Husbands and families should be targeted with massive education campaigns to support women and know that breast cancer diagnosis does not mean death. Women and their husbands should be informed that early breast cancer is highly curable with partial breast surgery without mutilation of mastectomy, radiation and adjuvant systemic therapy. Prevention and screening for locally advanced breast cancer should be a priority in most Arab countries. It can be achieved with breast self-examination, clinical breast examination, continuous awareness campaigns and advocacy efforts, and new clinical programs and initiatives with training of social workers and nurses to teach and examine breasts of women in their homes and community centers 2. This is applicable in all Arab countries. In countries where resources are available, screening mammography is recommended starting age 40. Early breast cancer is treated by primary surgery. Women should be offered the choice of partial mastectomy with radiation therapy, or modified...
radical mastectomy. Comfortably negative margins are important in young women because of higher risks of local recurrence. Reconstruction is important. Sentinel lymph node biopsy needs expertise, training and equipment and reduces long term lymphedema. Training and expertise of surgeons for SLNB is important. Adjuvant therapy includes chemotherapy, targeted therapy, and hormonal therapy. Locally advanced breast cancer is treated with neoadjuvant pre-operative therapy. Radiation therapy centers in Arab countries lack in numbers and are mostly distributed in major cities and make it less available for many women who may be otherwise candidates for partial mastectomy and radiation therapy. Guidelines for low and middle-income countries are published and readers are also referred to the special supplement published in Cancer by the Breast Health Global Initiative 3-6

References


Recent Advances in Radiotherapy of Localised Prostate Cancer

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Localized prostate cancer (PC) includes cases of cancer confined to the organ (T1,T2) and those with minimal extra capsular spread (T3) and without nodal metastasis and no distant spread. Treatment options include watchful waiting, radical prostatectomy (RP), brachytherapy (BT) or external radiotherapy (ERT) with or without androgen deprivation therapy (ADT). Criteria of treatment selection depend on three main factors, namely the overall life expectancy of the patient as determined by his age and co-morbidity, the biological characteristics of the tumor with its predictive behavior and on the preference of the patient with consideration of relative efficacy, adverse effects and quality of life issues. However in good proportion of cases (>30%) treatment is mis-matched as patients might not be receiving the most appropriate treatment (1).

Radical prostatectomy (RP) remained the standard of care for many decades with expected 10 years incidence free from PSA failure of 50-75%. However, RP suffers from serious complications as stress incontinence (8-30%) and impotence (100% in non-sparing RP).

Results of conventional RT used to be inferior to RP with 10 years PSA free survival of 55-60%. However, with much less serious complications (2,3). These inferior results were mainly due to patient selection in RT (mainly those unfit for RP) and to relatively lower dose to prostate (60 Gy) due to limitations imposed by equipments and sensitivity of organs at risk (OAR) that can not be well protected during RT. During the last few decades there were rapid developments in 3D imaging (CT & MRI), fast 3D dose calculations, more accurate dose delivery, rigid patient immobilization, accurate dose delivery as well as verification of treatment given. These advancements made it possible to give ERT with higher precision which allowed for dose escalation (76-80 Gy) and at the same time reducing doses to OAR. High precision RT for PC requires high energy digital accelerator with beam shaping device (MLC) for conformal RT, non-uniform beam fluence for intensity modulated RT (IMRT), electronic portal image (EPID) and more recently image guided RT to account for organ mobility. Modern imaging machines, well-trained staff and quality assurance for equipments and patient planning are essential pre-requisites. The adoption of these recent technologies resulted in significant improvements of results of treatment of PC and meanwhile reduced significantly the severity and frequency radiation-induced complications and improved the QL of these patients.

Results of modern RT are now comparable to those of RP with less side effects and better QL (4).

Very recently several investigational radiation techniques are introduced and are under clinical trials e.g. pre and post-operative irradiation in high-risk cases (6&7), proton beam therapy (8), neutron therapy and tomotherapy (9).

The most important questions to be asked regarding these investigational therapies are they improving the therapeutic ratio and are they cost-effective?

Further research along these lines will give an answer in due time.

References

7. Scott et al Radiother Oncology 2008;88:1-9
Carcinoma of Unknown Primary (CUP): Diagnosis and Treatment

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Epidemiology

Incidence and mortality
The definition of carcinoma of unknown primary (CUP) includes patients who have histologically confirmed metastatic cancer in whom a detailed medical history, complete physical examination including pelvic and rectal examination, full blood count and biochemistry, urinalysis and stool occult blood testing, histopathological review of biopsy material with the use of immunohistochemistry, chest radiography, computed tomography (CT) of the abdomen and pelvis and, in certain cases, mammography fail to identify the primary site. Carcinoma of unknown primary (CUP) is the seventh to eighth most frequently occurring cancer in the world and the fourth commonest cause of cancer death in both males and females. CUP accounts for some 2.3–4.2% of cancer in both sexes.

The annual age-adjusted incidence per 100,000 population in USA is 7–12 cases, in Australia 18–19 cases and in the Netherlands 5.3–6.7 cases. The median age for occurrence is around 60 years and CUP is marginally more frequent in males.

Aetiology and risk factors

In this heterogenous group of tumours, most of which follow an aggressive biological and clinical course, there are no obvious aetiological or risk factors that contribute to the pathogenesis of this syndrome.

Early diagnosis

Early detection of CUP is not possible. Therefore, no current screening programmes are available.

Pathology and biology

Almost 50% of patients with CUP will be diagnosed with metastatic adenocarcinoma of well to moderate differentiation, 30% with undifferentiated or poorly differentiated carcinomas, 15% with squamous cell carcinomas and the remaining 5% will have undifferentiated neoplasms. Immunohistopathological studies can be utilised to further characterize the undifferentiated neoplasms, poorly differentiated carcinomas, neuroendocrine tumours, lymphomas, germ cell tumours, melanomas, sarcomas and embryonal malignancies.

In children, embryonal malignancies make up the majority of the rare cases of disseminated malignancies without an identified primary tumour.

Biology

CUP is a heterogeneous group of tumours. There is no evidence regarding whether CUP carries a distinct biological entity involving specific genetic and phenotypic alterations.

The issue has not been extensively investigated on a molecular basis, and the limited information available is still controversial and inconclusive.

In general, CUP follows an aggressive biological and clinical behaviour.

Chromosomal and molecular abnormalities

Chromosomal abnormalities have been detected in the short arm of chromosome 1 including deletion of 1p, translocations with a breakpoint at 1p, isochromosome 1q and evidence for gene amplification. Identical results have also been reported in other advanced malignancies. Similar chromosomal abnormalities have been found in the short arm of chromosome 12. The isochromosome i(12)p or a deletion in 12p – a germ cell chromosomal marker – was observed in 25% of patients with poorly differentiated carcinoma and predominant lymph nodal disease.

Chromosomal instability (aneuploidy) was found in 70% of patients with metastatic adenocarcinoma or undifferentiated carcinoma.

In one study, overexpression of c-myc, ras and c-erB-B2, as demonstrated by immunohistochemistry, was reported in 96%, 92% and 65% of cases, respectively. However in another study c-erB-B2 expression was found in 11% of patients with poorly differentiated carcinomas and. Additionally, using immunohistochemistry bcl-2 and p53 were overexpressed in 40% and 53% of cases, respectively, whereas using PCR only 26% of patients expressed p53. Furthermore, the incidence of p53 mutations was 26% of the cases studied. Strong EGFR expression was observed in 12% of patients, but no evidence of EGFR exon 18, 19, and 21 amplification was detected. Strong expression of VEGF and stromal TSP-1 was seen in 83% and 20%, respectively. MMP-2, MMP-9 and TIMP-1 are widely expressed in CUP patients, suggesting an essential role of proteolysis in these tumors.
Diagnosis

Diagnostic evaluation for the identification of primary site and staging
Despite extensive work-up, less than 20% of patients with CUP have a primary site of their cancer identified ante-mortem. Autopsy studies have reported that 70% of cases remained undiagnosed.

Diagnostic pathology
An adequate sample of tumour tissue is essential for carrying out light microscopy examinations, immunohistochemical investigations, evaluating other markers or receptors as well as performing more specific investigations such as electron microscopy or genetic/molecular studies. Light microscopy can only characterize cell morphology and tumour differentiation. Immunohistochemical studies are of paramount importance. Several cell components can be identified by the immunoperoxidase technique using a series of monoclonal or polyclonal antibodies to enzymes, structural tissue components (i.e. cytokeratins), hormonal receptors, hormones, oncofetal antigens or other substances. For metastatic adenocarcinomas a simplified diagnostic panel of only 10 markers has been developed. These markers are: CA 125, CDX2, cytokeratins 7 and 20, estrogen receptor, gross cystic disease fluid protein 15, lysozyme, mesothelin, PSA and thyroid transcription factor 1. Electron microscopy should be considered in the evaluation of poorly differentiated neoplasms in young patients, particularly when immunoperoxidase stains are inconclusive.

Cytogenetic analysis could be useful in the evaluation of young patients with poorly differentiated carcinomas or undifferentiated neoplasms potentially responsive to chemotherapy, i.e. identification of isochromosome i(12p) in poorly differentiated carcinoma with lymph nodal midline distribution, of translocation t[11; 22] (q24; q12) in peripheral neuroectodermal tumour and Ewing’s sarcoma, of t[8; 14] (q24; q32) in non-Hodgkins lymphomas, of t[3; 13] in alveolar rhabdomyosarcoma or of 3p deletion in small cell lung carcinoma.

Diagnostic molecular technology
Identification of primary site by multiple gene expression profiling (DNA microarrays platforms) carries a relatively high specificity and sensitivity, however its potential therapeutic or prognostic benefit remains questionable.

Diagnostic radiology
In terms of conventional radiology, a routine chest radiograph is part of the initial evaluation of the patient with CUP. CT of the abdomen and pelvis results in the detection of a primary site for the cancer in 30–35% of patients. CT of the chest has not been adequately studied. CT scans can also be helpful in evaluating the stage of the disease. Mammography has been recommended for female patients with metastatic adenocarcinoma involving axillary lymph nodes. Magnetic resonance imaging was found to be very sensitive for the detection of mammographically occult breast cancer. FDG-PET scans are a valuable modern imaging technique for patients with CUP, particularly for patients with squamous pathology involving the cervical lymph nodes.

Diagnostic endoscopy
Endoscopic studies should always be directed towards investigating specific symptoms or signs. For example, patients with pulmonary symptoms and/or indications for imaging should be offered fiberoptic bronchoscopy, or patients with abdominal symptoms or occult blood in the stool should be investigated with gastrointestinal endoscopies.

Diagnostic value of serum tumour markers
Serum β-chorionic gonadotropin (b-HCG), α-fetoprotein (AFP) and prostate specific antigen (PSA) should be requested for male patients with CUP, in order to exclude treatable extragonadal germ cell tumours and metastatic prostate cancer. High levels of serum thyroglobulin in CUP patients with bone metastases is indicative of an occult thyroid cancer. In certain sub-sets, such as those with isolated axillary nodal metastatic disease and in peritoneal papillary adenocarcinomatosis, serum CA 15-3 and CA 125 could be of some help.

Staging

Clinicopathological sub-sets
It is very important to classify CUP patients into established clinicopathological sub-sets in order to guide diagnostic approaches and to be able to offer optimal therapeutic management. The classification of the different clinicopathological entities is shown in table 1.

Prognosis

Prognostic and predictive factors
Median survival in CUP patients enrolled in clinical studies ranges from 6 to 10 months, but in an unselected CUP population outside a clinical trial, life expectancy is only 2–3 months. The prognostic and predictive factors examined in two available studies include age, gender, performance status, weight loss, histopathology, tumour burden, tumour location, number of metastatic sites and serum markers. The factors characterized as significant were certain histopathological sub-sets (poorly differentiated carcinoma, squamous cell carcinoma, and neuroendocrine carcinoma), number of metastatic lesions (≤2), female sex, performance status, weight loss and various serum markers (alkaline phosphatase, LDH, and CEA). The detection of these prognostic and predictive factors helped to distinguish the favourable from the unfavourable groups of CUP patients.

Treatment

Overall strategy
Treatment recommendation for CUP patients is based on a type 3 level of evidence and available treatment options are considered as suitable for individual clinical use or investigational. For adequate therapeutic guidance CUP entities should be categorized into favourable or unfavourable sub-sets. Some favourable sub-sets require specific treatment approaches and have the potential for an excellent treatment outcome. The favourable and unfavourable sub-sets of CUP are illustrated below.

Favourable sub-sets
1. Poorly differentiated carcinoma with midline distribution (extragonadal germ cell syndrome).
2. Women with papillary adenocarcinoma of the peritoneal cavity.
3. Women with adenocarcinoma involving only axillary lymph nodes.
4. Squamous cell carcinoma involving cervical lymph nodes.
5. Isolated inguinal adenopathy (squamous carcinoma).
6. Poorly differentiated neuroendocrine carcinomas.
7. Men with blastic bone metastases and elevated PSA (adenocarcinoma).
8. Patients with a single, small, and potentially resectable tumour.

Unfavourable sub-sets
1. Adenocarcinoma metastatic to the liver or other organs.
2. Non-papillary malignant ascites (adenocarcinoma).
3. Multiple cerebral metastases (adeno or squamous carcinoma).
4. Multiple lung/pleural metastases (adenocarcinoma).
5. Multiple metastatic bone disease (adenocarcinoma).

Treatment of favourable groups

Poorly differentiated carcinoma with midline distribution (extragonadal germ cell syndrome)
This sub-set of CUP should be managed in a manner similar to poor prognosis germ cell tumours with platinum-based combination chemotherapy, on a type 3 level of evidence. More than 50% response has been reported, with 15–25% complete responders and 10–15% long-term disease-free survivors.

Women with papillary adenocarcinoma of peritoneal cavity
These patients should optimally be treated as FIGO stage III ovarian cancer with aggressive surgical cytoreduction followed by platinum-based postoperative chemotherapy, on a type 3 level of evidence. Survival is identical to FIGO stage III ovarian cancer patients.

Women with adenocarcinoma involving only axillary lymph nodes
In these patients, locoregional treatment with or without systemic therapy is suggested. The management is similar to that of stage II or III breast cancer. In patients with N1 disease (mobile nodes) axillary clearance followed is either a simple mastectomy or breast radiotherapy is recommended. In premenopausal women with positive oestrogen receptors, adjuvant chemotherapy followed by tamoxifen administration is recommended. For postmenopausal patients with positive oestrogen receptors tamoxifen is still recommended. No data are available concerning adjuvant chemotherapy in these patients. In patients with N2 disease (fixed nodes), preoperative neoadjuvant chemotherapy is suggested following the guidelines for stage III breast cancer. However, in non-responding tumours or in elderly patients, radical radiotherapy should be the treatment of choice. Oestrogen receptor positive patients should continue on tamoxifen treatment. All the above data are on a type 3 level of evidence. The reported 5- and 10-year overall survival rates are 75% and 60%, respectively.

Squamous cell carcinoma involving cervical lymph nodes
These patients should be treated with locoregional management according to the guidelines for locally advanced head and neck cancer. The 5-year survival rates range from 35 to 50% with documented long-term disease-free survivors, on a type 3 level of evidence.

Surgery alone is inferior and can be recommended only in selected patients, particularly those with pN1 neck disease with no extracapsular extension.

Radiotherapy to the ipsilateral cervical nodes alone is still inferior to extensive irradiation to both sides of the neck and the mucosa in the entire pharyngeal axis and larynx. Whether such an intensive irradiation prolongs survival is still uncertain.

Although the role of systemic chemotherapy remains undefined, concurrent chemoradiotherapy seems to be beneficial particularly in patients with an N2 or N3 lymph node disease.

Isolated inguinal lymphadenopathy from squamous cell carcinoma
Inguinal node dissection, with or without local radiotherapy, is the recommended treatment for this sub-set of patients on a type R basis. Long-term survivors have been reported.

Poorly differentiated neuroendocrine carcinomas
This group of CUP patients should be treated with platinum-based or paclitaxel/carboplatin-based chemotherapy on a type 3 level of evidence. The reported response rates are as high as 50–70% with 25% complete responders and 10–15% long-term survivors.

Men with blastic bone metastases and elevated PSA from an adenocarcinoma
This rare sub-set of CUP patients, although still debatable, should be considered as having metastatic prostate cancer and endocrine treatment is recommended as the initial therapy on a type R basis.

CUP patients with a single small metastasis
Local treatment with either resection and/or radiotherapy should be recommended on a type R basis. A considerable number of these patients enjoy palliative benefit and some of them a long disease-free survival.

Treatment of unfavourable groups

No chemotherapy regimen has been found convincingly effective for the majority of CUP patients presenting with disseminated bone, liver or multi-organ metastases of adenocarcinoma. Despite some evidence of response, median survival is still in the range of 8–9 months, although some slight differences in 1, 2 or 3 years survival have been reported. Chemotherapy regimens used include platinum or taxane/platinum combinations, on a type 3 level of evidence. Randomized studies have shown similar activity between platinum combined with gemcitabine or irinotecan as well as between platinum- and taxane-based chemotherapy, on a type 2 level of evidence. Only investigational treatment options apply to these patients. Alternatively, low toxicity chemotherapy of palliative intent or best supportive care should be considered.

Second-line chemotherapy
Second-line chemotherapy with various regimens in patients who have failed platinum-based treatment has been reported to be ineffective, on a type 3 level of evidence. Early data with targeted treatment (bevacizumab and erlotinib) showed substantial activity and acceptable tolerance on a type 3 level of evidence.

Late sequelae
Late sequelae related to surgery, radiation therapy and chemotherapy
Clinically significant long-term sequelae related to surgery in specific CUP sub-sets, i.e. in women with adenocarcinoma involving axillary lymph nodes or in women with papillary adenocarcinoma of peritoneal cavity or in patients with squamous cell carcinoma involving cervical lymph nodes, are no different from the relevant surgical late complications of patients with known primary breast, ovarian or head–neck cancers of similar clinical stages. Clinically long-term sequelae related to radiation therapy in women with adenocarcinoma involving axillary lymph nodes or in patients with squamous cell carcinoma involving cervical lymph nodes are similar to those of known primary breast and head-neck cancers. In a majority of patients late sequelae attributable to chemotherapy do not represent a clinical problem since median survival is no longer than 1 year. In the minority of patients with long-term survival late toxicities are similar to those seen in patients treated with platinum- and/or taxane-based chemotherapy.

Follow-up

The short life expectancy of CUP patients leaves little room for developing guideline recommendations for a follow-up strategy. As a general rule, after completion of treatment, patients in sub-sets with a poor prognosis should attend outpatient clinics upon need, but patients with a favourable CUP sub-set diagnosis should be seen on a regular basis similar to that followed for the respective solid tumour, such as germ-line tumours for patients with middle line distribution, ovarian cancer for carcinomatosis peritonei in women and breast cancer for patients with axillary nodal metastases.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Histology</th>
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<tr>
<td>Liver (mainly) and/or other organs</td>
<td>AdenoCa moderately or poorly differentiated</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Undifferentiated or poorly differentiated Ca</td>
</tr>
<tr>
<td>Mediastinal–retroperitoneal (midline distribution)</td>
<td>AdenoCa well to poorly differentiated</td>
</tr>
<tr>
<td>Axillary</td>
<td>Squamous cell Ca</td>
</tr>
<tr>
<td>Cervical</td>
<td>Undifferentiated Ca, squamous, mixed squamous/adenocAa</td>
</tr>
<tr>
<td>Inguinal</td>
<td>Papillary or serous adenoCa (epithelial bodies)</td>
</tr>
<tr>
<td>Peritoneal cavity</td>
<td>Macrophage-producing adenoCa moderately or poorly differentiated (asignet ring cells)</td>
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<tr>
<td>Peritoneal adenosarcomatosis in females</td>
<td>Malignant ascites of other unknown origin</td>
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<tr>
<td>Malignant ascites of other unknown origin</td>
<td>Lungs</td>
</tr>
<tr>
<td>Pulmonary metastases</td>
<td>AdenoCa of various differentiations</td>
</tr>
<tr>
<td>Pleural effusions</td>
<td>AdenoCa moderately or poorly differentiated</td>
</tr>
<tr>
<td>Bones (solitary or multiple)</td>
<td>AdenoCa of various differentiations</td>
</tr>
<tr>
<td>Brain (solitary or multiple)</td>
<td>AdenoCa of various differentiations or squamous cell Ca</td>
</tr>
<tr>
<td>Neuroendocrine tumours</td>
<td>Poorly differentiated Ca with neuroendocrine features (mainly), low-grade neuroendocrine Ca, small cell anaplastic Ca</td>
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<tr>
<td>Malignant melanoma</td>
<td>Undifferentiated neoplasm with melanoma features</td>
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References

Prognostic Factors of Adult Acute Lymphoblastic Leukaemia and its Impact on the Treatment Outcome


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Background

A substantial progress has been made in the management of acute lymphoblastic leukemia over the last two decades. The aim of this study was to assess the prognostic factors of our adult ALL patients and their correlation to treatment outcome, leukemia free survival and overall survival.

Patients and Methods

Hundred and fifteen patients were included in this study conducted at the Medical Oncology Department – NCI .Cairo in the period between 1999 to 2004. The diagnosis was ALL in all patients. The patients were stratified according to their prognostic factors into standard, high, and very high risk groups. Mature B phenotype were excluded and treated with a separate protocol. The treatment plan included: Prephase for patients with high TLC and/or organomegaly. Induction phase I: Four drugs: Vincristine, Doxorubicin, L-Asparaginase and prednisone with intrathecal MTX. Patients that attained CR were subjected to cranial irradiation with 24 Gy and intrathecal MTX for four injections. Phase II induction with Cyclophosphamide and Cytarabine.

Consolidation phase I: Vincristine, Doxorubicine and prednison with Triple intrathecal. Phase II consolidation: Cyclophosphamide, Cytarabine and Etoposide with triple intrathecal. Maintenance therapy: two years with 6 mercaptopurine and methotrexate. For patients with high and very high risks, one cycle of high dose cytarabine and mitoxantrone (HAM regimen) was added between induction and consolidation. Very high risk patients with available donor were referred to transplantation in CR1. Informed consents were signed by all cases.

Results

The median age was 25 years (range 16-60). The study included 73 males and 42 females. CNS involvement at presentation was reported in 14 cases (12.2%). Immunophenotyping were pro B (7%), C. ALL & Pre B (56.5%) and T phenotype (20.9%). The BCR-ABL fusion gene transcript was positive in 15 cases and ALL1-AF4 fusion genes transcripts was reported in 3%. Forty five patients (39.1%) reported to have standard risk, while 55 (47.8%) and 15 (13%) were high and very high risk respectively. Complete remission was achieved in 76.5% (n = 88) while 23.5 % (n=27) showed no CR. The CR rate of the standard risk group was 88.9% versus 70.9% and 60% for the high and very high risk respectively (p=0.029). The median survival for all patients was 14 months (95% CI, 9.2 to 18.8). Survival at 60 months was 28.24 %, it was 34%, 21% and 20.1% for the standard, high and very high risk respectively (P=0.017). There was significant difference in survival between patients with pro-B, pre-B&CALL, and T phenotype (p=0.0019). The median time to progression was 16 months (95% CI, 13.5 to 18.5). At 60 months 35.2% were still in remission. Time to progression was 44, 12 and 14 months for the standard, high and very high risk groups respectively (p=0.047). Time to progression between patients with Pro-B, pre-B&C-ALL, and T phenotype were 3, 17 and 16 months respectively (p=0.0007).

Conclusion

The CR rate, LFS and survival of the standard risk are satisfactory while those of the high and very high risk are still in need to be improved, whether we can achieve this by higher post remission chemotherapy, targeted therapy or stem cell transplantation remains to be investigated in our ongoing protocol.
Chronic Lymphocytic Leukemia Diagnosis and Prognosis: A Descriptive Analysis for 41 Patients

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Background

The new guidelines from the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) have important implications for diagnosis, identification of prognostic factors and assessment of the patient’s response to treatment, and demonstrate the increasing importance of the haematopathology laboratory in the management of individual patients with chronic lymphocytic leukemia (CLL) (Hallek M, Cheson BD, Catovsky D et al; 2008). They emphasize the key role played by a range of investigations, such as Flow cytometric immunophenotyping and fluorescence in situ hybridization (FISH) analysis. Immunophenotyping (IPT) is indispensable for the diagnosis of mature B-cell lymphoid neoplasms through the identification of phenotypically abnormal cells belonging to the B-cell lineage and recognition of phenotypes characteristic of separate disease entities. In addition, flow cytometry can be used to identify expression of targets for potential antibody-directed therapy such as CD52, CD23 and CD80 and provide some additional prognostic information such as CD38 expression in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (Fiona E. Craig and Kenneth A. Foon, 2008). In 2000, Döhner and colleagues used FISH analysis to demonstrate del 13q14, del 17p13 and Trisomy 12. Twenty four (58.8%) patients were Males and 17(41.5%) Females; Median age 55(range 44-71).

Results

According to the CLL scoring system 38(92.3%) patients were in score 5 and 3(7.3%) in score 4. CD38 was expressed in 19(46.4%) out of 41 patients and 22(53.4%) were negative. Del 13q14; del 17p13 (P53); Trisomy 12 done by FISH on the available cultures was found positive in 6 (60%); 2(20%) and 4(40%) out of 10 patients respectively and were found negative in 4(40%),8(80%).6(60%) respectively.

Aim

Prognostic factors analysis (IPT and FISH) should be used to identify patients who are likely to have a good outcome as well as those expected to have an adverse outcome.

Patients and Methods

We retrospectively analyzed IPT of 41 CLL patients presented to our unit from February 2006 through March 2009. Flow cytometry was performed for all CLL cases using the standard protocols (CD 5/19, CD23, FMC7, CD79b, kappa/lambda and CD38). Florescence labeled antibodies were obtained from (Becton Dickinson, U.S.A) and run on FACSCALIBER using CELLQUEST software. Chromosomal cultures was available for 10 CLL patients on which FISH analysis was done to detect del 13q14, del 17p13 and Trisomy 12. Twenty four (58.8%) patients were Males and 17(41.5%) Females; Median age 55(range 44-71).
Acute Promyelocytic Leukaemia (APL) in 19 Egyptian Patients

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Background

Acute promyelocytic leukemia (APL) is now the most curable subtype of acute myeloid leukemia in adults. All-trans retinoic acid (ATRA), which induces differentiation of the leukemic cells into mature granulocytes, represents the important advance. The incorporation of ATRA in induction results in a high complete remission rate (CR) and decreases the relapse rate compared with treatment with chemotherapy alone (Martin S. Tallman, et al; 2002).

Aim

Evaluation of the effect of ATRA on the outcome of t (15:17) positive patients.

Patients and Methods

The diagnosis of APL was done according to the World Health Organization classification system. Morphological view confirmed the diagnosis of APL. The immunophenotypic features including human leukocyte antigen -DR, CD 34, CD 13 and CD 33 (Becton Dickinson, U.S.A) were performed. We performed chromosomal analysis and fluorescence in situ hybridization (FISH) of the bone marrow cells at diagnosis, the probe used for FISH LSI PML/RARA dual color, dual-fusion translocation probe (Vysis Inc., USA). Nineteen APL patients presented to our unit between 2005 and 2008, 9 Males and 10 Females; Median age 30, range (13 to 40). Seven patients were morphologically APL but were t (15:17) negative and were excluded. Twelve were t (15:17) positive and received Induction chemotherapy in the form of Adriamycin for 3 days combined with ATRA for 3 months. Patients who achieved CR received 3 cycles of Consolidation in the form of Adriamycin for 3 days every 3 weeks followed by Maintenance chemotherapy using methotrexate, 6-mercaptopurine and ATRA. Patients were kept under follow-up.

Results

We analyzed 12 APL patients receiving ATRA, 7(58.3%) achieved complete cytogenetic remission (CCR) after an average of 3 to 6 months of starting treatment and they are still under follow up, 2 (16.6%) patients died during the course of treatment and 3 (25%) lost follow-up.

Conclusion

Historically, APL was fatal for most patients. However, the introduction of ATRA as targeted therapy for APL has dramatically improved the outcome of this disease. With contemporary therapeutic strategies, it appears that a cure rate of more than 50% is a reasonable expectation. ATRA has most dramatically changed the clinical course of a disease from one that was highly lethal to one that now appears highly curable.
Epidemiology

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, causing 500,000 deaths yearly (1). The continued risk factors that are mostly responsible for the rising incidence of HCC in the Arab world is hepatitis C (HCV). Egypt has the highest prevalence of HCV worldwide (2). Recently calculated weighted mean prevalences of Hepatitis B (HBV) and HCV were 6.7% and 13.9% among healthy populations, and 25.9% and 78.5% among HCC cases in Egypt. Among HCC cases, HBV significantly decreased over time (p=0.001) while HCV did not. Similarly there has been a three-fold increase in the age-adjusted rates for HCC in the western world, up to 7 per 100,000 has been observed (3), and is reportedly explained by the increasing incidence of hepatitis C that has been observed in North America and Europe during in the 80’s and early 90’s. Another more commonly recognized risk factor is non-alcoholic-steatohepatitis (NASH). NASH related HCC appear to occur in morbidly obese patients, whose relative risk of death from HCC is 4.52 times higher among men and 1.68 times higher among women, with a body mass index (BMI) ≥ 35, (4). NASH caused HCC is also noted among diabetics who are at increased risk of developing HCC (5).

HCC: Two Diseases in One

In most cases cirrhosis is a direct causative reason and contributes to the morbidity and mortality associated with HCC, thus HCC is essentially two diseases in one. Assessing those two aspects of the disease is imperative. The Child-Pugh scoring system of cirrhosis remains the most commonly used scoring system used by medical oncologists and hepatologists (6-7).

The Child-Pugh score depends on the allocation of 1 to 3 points depending on severity of five parameters: bilirubin, albumin, prothrombin time, clinical ascites, and clinical encephalopathy. Obviously the Child-Pugh scoring system does not account for the stage of cancer, a major limitation that led to the development of many other scoring systems that attempted at evaluating the two aspects of HCC: the cancer itself and the associated cirrhosis.

The Cancer of the Liver Italian Program (CLIP) score was defined and verified prospectively in HCC patients with predominantly a hepatitis C etiology (8). The CLIP includes the Child-Pugh score parameters, plus an assessment of tumor extent in the liver, the presence or absence of portal vein thrombosis, and the level of alpha-fetoprotein (AFP). The Chinese University Prognostic Index (CUPI) scoring system was developed in HCC patients with predominantly a hepatitis B etiology (9). The CUPI parameters are bilirubin, ascites, alpha-fetoprotein, alkaline phosphatase, the tumor extent as defined by the TNM staging system, and the absence or presence of clinical symptoms on presentation.

Other scoring systems include the Groupe d’Etude et de Traitement du Carcinome Hepatocellulaire (GRETCH) staging system (10), the Okuda staging system (11); the Japan Integrated Staging (JIS) Score (12), which is based on the TNM staging of the Liver Cancer Study Group of Japan (LCSGJ); and the Barcelona Clinic Liver Cancer (BCLC) classification system (13), which was recently validated prospectively (14).

In a retrospective analysis of patients with advanced HCC seen by medical oncologists at Memorial Sloan-Kettering Cancer Center between 2001-2006, we attempted to identify which of these eight scoring systems would be most valuable in this specific clinical setting (15). Using three statistical tools, c-index, the likelihood ratio test and the Akaike Information Criterion, the CLIP scoring systems performed best and this was compatible with the findings of Collete et al. (16). Obviously, this conclusion is limited by the retrospective nature of this analysis and needs to be further validated. On the practical level, using the Child-Pugh scoring system provides most of the information needed for risk-stratifying patients although the CLIP may be more informative in regard to prognosis.

Treatment

There is a continued emergent need for active therapies for advanced HCC considering that most patients present with advanced unresectable or metastatic HCC. In addition 50% of resected patients suffer recurrence within two years and require a systemic therapeutic approach (17). Chemotherapy single agents and in combinations have been tested extensively in HCC. Despite reported responses typical of phase II studies, and ranging between 10-20%, no study has shown an impact on survival (18-21). Given the disappointing results of single-agent therapies, combination regimens have also been investigated. A regimen combining cisplatin, interferon, doxorubicin, and 5-fluorouracil (PIAF) yielded a response rate of 26% and a median survival of 9 months in a recently reported single-arm phase II trial (22). In that study, of the 13 patients (26%)
who had a partial response, 9 underwent surgery, and 4 (9%) were found to have had a complete pathologic response to chemotherapy. This study suggests that chemotherapy contrary to the fact, works in some patients with HCC, considering that pathologic complete response was achieved in four cases. This data was also encouraging enough to consider evaluating PIAF as part of a large randomized study which was later performed yet did not show any improvement in survival when compared to single agent doxorubicin (23). And lastly, the data raise the possible use of PIAF in the surgical conversion setting. This approach has already been in use and would be recommended in that specific setting of medically fit patients with good liver function in whom cytoreduction is necessary to permit resectability. These conditions would justify the risk of the high toxicity of the regimen as an acceptable trade-off for potential curability of resectable tumors as part of a multi-disciplinary discussion.

**Targeted Therapies in HCC**

Other than the discouraging results of chemotherapy and the urgent need for active therapies, studying novel targeted agents seems a reasonable approach considering the presence of several molecular targets involved in the development of HCC. Of those is the Epidermal Growth Factor Receptor (EGFR) whose importance in HCC remains controversial (24-26). The most intriguing results are reported in a phase II study of erlotinib, which showed a 32% 6 months progression-free-survival, with 3 partial responses (8%) and a median overall survival of 13 months (27).

Considering the highly vascular nature of HCC (28-29) anti-angiogenic therapies have been studied extensively in this disease. Sorafenib is a novel molecular targeted agents that inhibits both pro-angiogenic (VEGFR-1, -2, -3; PDGFR-β) and tumorigenic (RET, Flt-3, c-Kit) receptor tyrosine kinases (RTKs). Sorafenib also inhibits the serine/threonine kinase Raf-1 in vitro (30). A phase II trial of sorafenib evaluating response in patients with advanced HCC showed 33.6% of patients had stable disease (≥16 weeks) commensurate with a median time-to-progression (TTP) of 4.2 months and the median overall survival of all patients was 9.2 months (31). Grade 3-4 treatment related toxicities included fatigue (9.5%), diarrhea (8%), and hand-foot skin reaction (5.1%). An interesting observation of central tumor necrosis noted in those patients with stable disease. The ratio of tumor necrosis and volume (N/V) was significantly associated with response, with responders having greater increases in the ratio between necrosis and tumor volume relative to baseline, as compared to non-responders (P=0.02) (32). This phase II study was followed by a large double-blinded, randomized phase III trial evaluating single agent sorafenib versus placebo in patients with advanced HCC and no more than Child-Pugh A cirrhosis (33). This trial demonstrated an improvement in survival of 10.7 months in the sorafenib group versus 7.9 months in the placebo group (p <0.001, HR= 0.69). The drug-related toxicity profile was comprised of 8% grade 3-4 diarrhea and hand foot syndrome. Despite the infrequency of bleeding events (< 1%), one should still use caution in this regard considering the anti-angiogenic nature of sorafenib.

A similar study was performed in Asia-Pacific and showed a statistically significant improvement (p=0.014) in survival was again noted in favor of sorafenib (6.5 month) versus placebo (4.2 months), similar to that noted in the SHARP trial but not to the same magnitude (34). It is worth noting that in the Asian study, patients who were accrued were more ill at start of therapy compared to the SHARP trial. These observations may partly or fully explain the difference in magnitude of benefit from sorafenib between those two populations. The impact of the hepatitis in the Asia-Pacific study pertaining to sorafenib remains un-addressed. Seventy-three per cent of patients accrued on the Asia-Pacific study had hepatitis B as an underlying risk factor, versus 18% of patients on the SHARP trial. From the SHARP trial, it is suggested that patients with hepatitis C may have an added advantage for sorafenib therapy (35). In a sub-group analysis of patients with hepatitis C based HCC, it was noted that these patients treated with sorafenib (n=93) had a median survival advantage of 14 months compared to the whole sorafenib treated group of 10.7 months. In contrast the placebo controlled hepatitis C group did not have any added survival advantage to the placebo population of the study, suggesting a possible positive influence of hepatitis C status on the efficacy of sorafenib. Of note, that the outcome of the 18% of patients with hepatitis B in the SHARP trial, remains to be reported. Similar advantage in favor of patients with hepatitis C and HCC who treated with sorafenib was noted in the phase II study (36).

The exciting results of those two studies apply to patients with preserved performance status and Child-Pugh A score. The safety and efficacy of sorafenib in patients with Child-Pugh B or C cirrhosis needs to be evaluated further. In the phase II study evaluating sorafenib in HCC (37), 28% of patients were Child-Pugh B cirrhosis. In 28 patients from which pharmacokinetic samples were obtained, AUC (0-8)(mg.h/L) was comparable between the Child-Pugh A (25.4) and Child-Pugh B (30.3) patients. Cmax (mg/L) were 4.9 and 6 Child-Pugh A and B patients respectively, with similar drug-related toxicity profiles. However, Child-Pugh B patients had worsening of their liver function more frequently, including transient increases of serum bilirubin, though it is unclear if this deterioration was drug-related or disease progression. Sorafenib acts as a substrate for UGT1A1, and the study did not collect direct bilirubin measurements, so it remains unclear if this total bilirubin elevation is due to worsening liver function caused by sorafenib or simply due to an inhibitory effect of UGT1A1 and decreased bilirubin glucuronidation. The safety of sorafenib in patients with HCC and advanced cirrhosis needs to be further studied. Sorafenib was also evaluated in combination with doxorubicin as part of a randomized double-blinded phase II study of doxorubicin plus sorafenib compared to doxorubicin plus placebo in chemotherapy-naive HCC patients (38). The primary endpoint, median TTP, was 9 months for the doxorubicin plus sorafenib arm and 5 months for the doxorubicin plus placebo arm. An exploratory comparison of overall survival between the two arms showed a significant difference of 13.7 months in favor of doxorubicin plus sorafenib versus 6.5 months for doxorubicin plus placebo (p=0.0049, HR=0.45). Grade 3-4 toxicities included fatigue (15%), and neutropenia (50%) in both arms. Sorafenib related toxicity included grade 3-4 diarrhea (11%) and grade 3-4 hand-foot syndrome (9%) in the combination arm. There was more left ventricular dysfunction in the doxorubicin plus sorafenib arm, having been reported in 19% of the cases (all grades) with 2% grade 3-4. A potential synergistic effect between doxorubicin and sorafenib leading to worsening cardiac function may exist and needs to be further elucidated. A larger randomized trial evaluating the combination versus sorafenib alone is underway.

Bevacizumab has been studied extensively in HCC, as a single agent (39-40), in combination with chemotherapy (41-43) and biologics (44). The most promising bevacizumab-doublet data is in combination with erlotinib (44). Patients with HCC and CLIP ≥ 3 were treated with bevacizumab and erlotinib. Based on an intent-to-treat analysis, 10 of 40 patients had radiographic responses The median PFS was 9 months, and the median overall survival was 15.6 months. Grade 3 and 4 fatigue and hypertension were each reported in 20 and 15% of the cases respectively. Similar grade gastrointestinal bleeds were reported in 12.5% of the cases. While these represent only pilot results and may reflect a select group of patients, the outcome of this study supports the biologic relevance of this combination of anti-angiogenic therapy and tyrosine kinase inhibitor in HCC. Sunitinib, a multi-targeted tyrosine kinase inhibitor, has also been tested in HCC.
Of 26 patients treated with sunitinib at 37.5 mg daily dose, 10 (38.5%) showed stability of disease, with a median PFS of 4.1 months. In this particular study, another study showed similarly promising results at the dose of 50 mg, with median TTP of 21 weeks and median OS of 45 weeks (46). Sunitinib is currently studied against sorafenib in a randomized phase III study (47).

References


Globally, breast cancer is the most common cancer among women, comprising 23% of all female cancers that are newly diagnosed in more than 1.1 million women each year.1 Breast cancer is the most common cause of cancer-related death among women worldwide, with case fatality rates highest in low- and middle-income countries (LMCs). Despite the common misconception that breast cancer is predominantly a problem of wealthy countries, 55% of breast cancer deaths each year in fact occur in developing rather than developed countries.2 More than 411,000 deaths each year result from breast cancer annually, accounting for more than 1.6% of female deaths from all causes.3 By 2010, the annual global burden of new breast cancer cases will rise to 1.5 million with an ever-increasing majority will be from LMCs. Approximately 4.4 million women diagnosed with breast cancer in the last 5 years are currently alive, making breast cancer the single most prevalent cancer in the world.1

Guideline development for breast cancer in LMCs

While evidence-based guidelines outlining optimal approaches to breast cancer detection, diagnosis, and treatment have been well developed and disseminated in several high-resource countries such as the U.S., these guidelines may be inappropriate to apply in LMCs for numerous reasons including inadequate personal resources, limited health care infrastructure, lack of pharmaceuticals, and cultural barriers. Hence, there is a need for clinical practice guidelines oriented toward LMCs, specifically considering and adapting to existing health care resources. The Breast Health Global Initiative (BHGI) has developed evidence-based, economically feasible, and culturally appropriate guidelines that can be used in nations with limited health care resources to improve breast cancer outcomes.4 Modeled after the approach of the National Comprehensive Cancer Network (NCCN), BHGI created and applied a consensus panel process now formally endorsed by the Institute of Medicine (IOM)5 to define resource-sensitive guidelines for breast cancer early detection,6 diagnosis,7 treatment,8 and health care systems,9 as related to breast health care delivery in LMCs. The BHGI guidelines are intended to assist ministers of health, policymakers, administrators, and institutions in prioritizing resource allocation as breast cancer treatment programs are implemented and developed in their resource-constrained countries.

Several key observations were made through the BHGI resource-stratified guidelines. Breast cancer outcomes correlate with the degree to which 1) cancers are detected early, 2) cancers can be diagnosed correctly, and 3) proper multimodality treatment can be provided in a timely fashion. Cancer prevention through health behavior modification may influence breast cancer incidence in LMCs.10 Diagnosing breast cancer at earlier stages is predicted to reduce breast cancer mortality. Programs to promote breast self-awareness and clinical breast examination and resource-adapted mammographic screening are important early detection steps.6 Screening mammography has been shown to reduce breast cancer mortality, but is cost prohibitive for most LMCs. Breast imaging, initially with ultrasound and, at higher resource levels with diagnostic mammography, improves preoperative diagnostic assessment and permits image-guided needle sampling.7 Comprehensive multimodality treatment including surgery, radiation, and systemic drug therapies, must be in place for the benefit of early cancer detection to be realized.8

The role of surgical excision in breast cancer diagnosis

While surgical excision for diagnosis can be used when alternatives are unavailable, needle sampling is highly preferable.11, 12 Under no circumstances should mastectomy be considered an acceptable method for tissue “sampling”.11 Fine needle aspiration biopsy (FNAB) is recognized to be the most cost effective procedure with the shortest turnaround time.13 The choice of sampling procedures (FNAB, core needle biopsy or excisional biopsy) should be based on the availability and access to cytopathologists/pathologists in each medical community, and the training and experience of the available pathology specialists.14

Surgical treatment for breast cancer in LMCs

The ability to perform a modified radical mastectomy (MRM), which includes surgical excision of the breast together with a level I/II axillary lymph node dissection, is considered a basic requirement for the management of patients with early stage breast cancer. The resources for surgical therapy are typically available in most medical settings that provide minimally advanced health care (Table 1). The availability of radiation therapy allows for consideration of breast conserving therapy, post-mastectomy chest wall radiation, and for the palliation of painful or symptomatic metastases.15
Lymph node metastasis is the single most important factor in assessing breast cancer prognosis and planning systemic therapy. Lymphadenectomy has therapeutic benefit for breast cancer patients, since axillary dissection renders regional control of axillary disease.16-18 The ability to perform a proper axillary dissection is a basic technique with which surgeons must be fully familiar in order to be able to provide comprehensive breast surgical care to breast cancer patients. However, lymph node dissection portends significant morbidity, with little or no therapeutic (as opposed to diagnostic) benefit if the nodes prove to be negative for cancer. Sentinel lymph node (SLN) biopsy, while developed in the context of high-income countries, actually can be used by breast surgery teams in lower income settings at low cost, when the technique is restricted to the use of blue dye without radiotracer.19

Surgical pathology as a key resource for breast surgery

Quality surgical pathology is critical to breast program function.7, 14 The availability of predictive tumor markers, especially ER testing, is critical to proper selection of cancer therapy when endocrine therapies are available, although quality assessment of immunohistochemical (IHC) testing is important to avoid false negative results. Interdisciplinary communication underlies the basis of success for breast diagnostic programs at all economic levels. Furthermore, the interaction of the pathologist with the radiologist and the surgeon (interdisciplinary team collaboration) is critical in the examination and reporting of the pathology specimen, since the clinical situation in which the specimen was obtained can markedly influence the significance of certain pathological findings, and in the case of cancer, can be critical in determining accurate tumor staging.

Management of locally advanced breast cancer

Despite the fact that breast cancer is the most common cancer among women in LMCs, these countries commonly lack early detection programs for breast cancer. As a result, women in LMCs commonly present with locally advanced breast cancer. Recent data shows that locally advanced breast cancer (LABC) and metastatic breast cancer are the most common stages at presentation, 60-80% of cases, in most LMCs.20-22 While the incidence of LABC has decreased significantly in developed countries with enhanced and maximal resources due to widespread education and increasing utilization of screening mammography,23 LABC remains a daily challenge for oncologists in LMCs where limitations to proper management include also lack of local data, cultural circumstances, and weak inefficient health care systems.

Preoperative chemotherapy is the preferred primary therapy for LABC, because it allows early assessment of sensitivity to treatment as well as breast conservation.23 Clinical assessment of chemosensitivity may be particularly helpful, because emerging data suggests that there could be differences in host metabolism of systemic treatment agents—tamoxifen, alkylating agents, taxanes—on genetic bases, with associated efficacy and toxicity differences among genetically different populations.24, 25 Research specifically directed at differences among groups in response to systemic therapy may be warranted.26 While the preferred initial treatment of LABC is systemic therapy, if optimal chemotherapy and evaluation are not available, then primary MRM is acceptable. However, it should be recognized that without systemic therapy, surgery alone for LABC is unlikely to improve outcome, given the high likelihood of systemic relapse, so the role of MRM without adjuvant treatment for LABC should be viewed primarily as palliative therapy. After responding to systemic therapy, most LABC patients will require an MRM followed by radiation therapy.27 Locoregional therapy decisions should be based on both the pretreatment clinical extent of disease and the pathologic extent of the disease after chemotherapy. Accordingly, physical examination and imaging studies that accurately define the initial extent of disease are required before treatment.28 The success of breast conservation after preoperative chemotherapy depends on careful patient selection and achieving negative surgical margins. Adjuvant breast radiation is indicated for all patients treated with breast conservation. For patients treated with mastectomy, chest-wall and regional nodal radiation should be considered for those who present with clinical stage III disease or have histologically positive lymph nodes after preoperative chemotherapy.28

Metastatic and inflammatory breast cancer should be initially managed with preoperative therapy irrespective of resource level. Standard preoperative therapy includes anthracycline-based chemotherapy. The addition of sequential taxane after anthracycline-based chemotherapy improves pathological responses and breast-conservation rates, though may not improve survival. The combination is considered appropriate treatment at the enhanced and maximal level; however, costs and lack of clear survival benefit do not justify its use at limited resource levels. CMF combination chemotherapy is less potent than anthracycline and taxanes, but may be used in its classical schedule in LMCs because of lower costs and lesser complications. The role for preoperative endocrine therapy remains to be better defined, but appears to be feasible and acceptable in elderly women.23

Training in breast surgery in LMCs

While the MRM is considered fundamental surgical training in high-income countries, surgeons from LMCs may have had less exposure to the procedure and may not be knowledgeable about the operation’s proper technical execution. A retrospective review of patients referred from outside institutions to Tata Memorial Hospital in Mumbai, India found that of 424 who had undergone “therapeutic” surgical interventions, 191 (45%) were judged to have incomplete surgery. Of these, 153 patients underwent completion revision surgery and 123 had residual axillary nodes including 64 patients (52%) with metastatic lymph nodes found to have been left behind in the axillary bed.29 Thus, surgical training in LMCs needs to address education regarding these fundamental oncologic surgical procedures.

Quality control measures and process metrics as tools for decision making

While resource stratified guidelines may provide a framework for systemic improvement in cancer care delivery, these guidelines are useful only if they are implemented and if that implementation success is in turn measured. Quality control measures need to be integrated into cancer care programs at all levels of early detection, diagnosis and treatment. Focusing efforts at improving performance in problem areas assures efficient resource utilization and maximizes positive impact. Non-punitive reporting of errors is a key step in improving patient safety. Proper methodology for defining quality improvement initiatives must be considered, and adapted to existing resources.30 Without metrics, it is difficult to determine programmatic success.

Process metrics are also useful tools for tracking progress and informing future decisions by policy makers. Carefully selected process metrics can be collected without excessive effort or cost and can be used to measure the effectiveness of a facility or country’s ability to detect, diagnose and treat cancer. Generally, the
References


Table 1. Breast cancer surgery checklist

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Strengths</th>
<th>Weakness</th>
<th>Required sources</th>
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<tr>
<td>Modified radical mastectomy (MRM)</td>
<td>Rapid treatment</td>
<td>Disfiguring.</td>
<td>Staff</td>
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<td>Curative for early breast cancer</td>
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<td>• Surgeon</td>
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<td>Technology to perform widely available</td>
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<td>• Anesthesiologist</td>
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<td>• Physiotherapist</td>
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<td>• Medical Social Worker /Counselor</td>
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<td>Surgical resources</td>
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<td>• Operating theater</td>
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<td>• Anesthetics</td>
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<td>• Post-operative care system</td>
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<tr>
<td>Breast conserving surgery with axillary dissection</td>
<td>Rapid surgical treatment</td>
<td>Technically demanding</td>
<td>Surgical staff and resources as above under MRM</td>
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<td>Not appropriate for all patients</td>
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<td>Requires ability to assess margin status by breast imaging and pathology</td>
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<td>Requires application of post-operative radiation therapy as potentially curative therapy for breast cancer</td>
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<td>SLN with blue dye</td>
<td>Allows for accurate identification of SLN</td>
<td>Requires experienced SLN team</td>
<td>Staff</td>
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<td></td>
<td>Minimizes post-surgical morbidity in women with negative axillary lymph nodes</td>
<td>Rare allergic reactions</td>
<td>• Experienced surgeon</td>
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<td></td>
<td></td>
<td>• Experienced pathologist</td>
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<tr>
<td>SLN with radiotracer</td>
<td>Allows for accurate identification of SLN</td>
<td>Requires experienced SLN team.</td>
<td>Staff</td>
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<td>Minimizes post-surgical morbidity in women with negative axillary lymph nodes</td>
<td>Special handling of radiotracer</td>
<td>• Experienced surgeon</td>
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<td>• Experienced pathologist</td>
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<td>Procedures, equipment, and facilities for radio tracer handling (nuclear medicine)</td>
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Targeted Therapy of HTLV-I Associated Adult T-cell Leukemia/Lymphoma: From the Bench to the Bedside

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Overview on ATL

Adult T-cell leukemia-lymphoma (ATLL) (reviewed in Bazarbachi and Hermine, 2001, Bazarbachi et al. 2004a) is an aggressive lymphoid proliferation associated with the human T cell lymphotropic virus type I (HTLV-I) (Hinuma et al. 1982). ATLL, the first human disease associated with a retroviral infection, usually occurs in native individuals from the HTLV-I endemic regions, i.e. the southern Japan, the Caribbean, inter-tropical Africa, Brazil and the Middle East (Gessain 1996). Although HTLV-I may be transmitted by intravenous route or sexual intercourse, vertical transmission through breast-feeding is required for ATLL development.

ATLL develops after a very long latency period in 3 to 5% of HTLV-I infected individuals, and is preceded by oligoclonal expansions of HTLV-I-infected activated T cells (Wattel et al. 1995). These clonal expansions, at least early after infection (Mortreux et al. 2001) result from the expression of the viral transactivator protein Tax, which activates the viral promoter and various cellular genes and creates an autocrine loop involving interleukin-2, interleukin-15 and their cognate receptors (Waldmann et al. 1985, Azimi et al. 1999). Tax alters many cellular pathways: it activates CREB/ATF, AP-1 and NF-κB, upregulates antiapoptotic proteins, represses p53, DNA polymerase beta, PCNA and MAD-1 and interferes with several cell cycle regulators including cyclins and cdk-inhibitors (reviewed in Franchini 1995, Yoshida 2001). Tax also influences the microenvironment: it induces the synthesis of TGF-β, inhibits TGF-β signal transduction in infected cells (Arnulf et al. 2002), induces angiogenesis, metalloproteinases and gap junction mediated communication between infected cells and endothelial cells, hence contributing to the extravasation and invasiveness of ATLL cells (El-Sabban et al. 2002, Bazarbachi et al. 2004b).

Among the impressive properties of Tax, activation of the NF-κB pathway plays a mandatory role in the proliferation and transformation of infected T cells (Yamaoka et al. 1998). NF-κB plays a central role in the regulation of immune and inflammatory responses (reviewed in Ghosh and Karin 2002, Li and Verma 2002). In unstimulated cells, NF-κB is found in an inactive cytosolic form, associated with an inhibitory subunit known as IκB. Upon cell stimulation, the IκB proteins are phosphorylated by the IκB kinase (IKK) complex, then ubiquitylated and subsequently degraded by the 26S proteasome. Consequently, Rel-A containing NF-κB proteins translocate to the nucleus, bind specific promoters, and activate gene transcription (reviewed in Ghosh and Karin 2002, Li and Verma 2002). HTLV-1-infected and Tax-expressing cells demonstrate constitutive nuclear expression of NF-κB (Mori et al. 1999). Tax is indeed a powerful stimulator of the NF-κB pathway, which acts at multiple levels to initiate and maintain NF-κB activation (reviewed in Kfoury et al. 2005). We recently demonstrated that the lysine residues located in the carboxy-terminal domain of Tax are critical for Tax ubiquitylation and Tax-induced NF-κB activation (Nasr et al. 2006). Specifically, we showed that these C-terminal lysines are important for Tax binding to IKK, IKK activation and nuclear translocation of NF-κB. We also showed that Tax is post-translationally modified by SUMO binding, and that sumoylation is critical for Rel A-enriched nuclear body formation and NF-κB activation (Nasr et al. 2006). Finally, we showed that K63-ubiquitylated Tax activates IKK in a centrosome-associated signalosome, leading to the production of Tax-free active cytoplasmic IKK (Kfoury et al. 2007). These observations highlight an unsuspected cellular and biochemical complexity in Tax-induced IKK activation and represent potential new targets for ATL therapy.

Targeted therapies for ATLL

Zidovudine and interferon alpha

ATL is an ideal model for targeted therapy because of its extremely poor prognosis due to chemotherapy resistance and to the presence in the leukemic cells of two well characterized targets: the HTLV-I oncoprotein Tax and the constitutive activation of the NF-κB pathway (reviewed in Shinoyama 1992, Bazarbachi and Hermine 2001, Bazarbachi et al. 2004). In multiple phase II clinical studies and more recently in a worldwide metaanalysis, we and others have shown that antiviral therapy using the combination of zidovudine (AZT) and interferon alpha (IFN) results in a high response and complete remission rates, resulting in impressive prolonged survival of more than 10 years in almost half of the patients (Gill et al., 1995; Hermine et al., 1995; Bazarbachi and Hermine, 1996). This targeted therapy is now considered as gold standard first line therapy. However, many patients eventually relapse, stressing the need for additional effective therapies (Hermine et al., 2002).

Arsenic trioxide

A very effective treatment for acute promyelocytic leukemia, arsenic trioxide (As) synergizes with IFN to induce G1 arrest and apoptosis in ATL (Bazarbachi et al., 1999) through shut-off of the NF-κB pathway and Tax degradation by the
proteasome (El-Sabban et al., 2000; Nasr et al., 2003). This combination yielded promising clinical results in relapsed/refractory ATL patients (Hermine et al., 2004). We recently demonstrated that the two agents cooperate to cure mouse ATL derived from these Tax transgenics and selectively eradicates leukaemia-initiating cells. Preliminary results from a phase II clinical study using a triple combination of arsenic, AZT and IFN are extremely encouraging.

Proteasome inhibitors
PS-341 is a selective inhibitor of 26S proteasome. PS-341 has demonstrated clinical effect in hematological malignancies. We demonstrated that PS-341 and its combination with doxorubicin or etoposide have a selective effect on fresh ATL cells and HTLV-I transformed cells, supporting a potential therapeutic role for PS-341, either alone or in combination with chemotherapy in patients with ATL and other HTLV-I negative T-cell lymphomas (Nasr et al., 2005). A study on another mice model of ATL showed that PS-341 synergises with the human monoclonal antibody targeting the interleukin 2 receptor and decreases the DNA-binding activity of NFκB by preventing the degradation of the α subunit of inhibitors of NFκB (Tan and Waldmann, 2002).

Inhibitors of angiogenesis
The important role of angiogenesis in the growth and metastasis of solid tumours is well established. The invasive nature of ATL with common visceral invasion, suggests a possible interaction between cells infected with HTLV-I and endothelial cells. We have shown that HTLV-I positive cells communicate with endothelial cells through paracrine stimulation and through direct heterocellular communication (El-Sabban et al., 2002). Furthermore, cells from ATL cells specifically secrete high concentrations of the angiogenic factors VEGF and b-FGF, induce formation of endothelial tubes in vitro and establish functional communication with endothelial cells through gap junctions. Interaction of HTLV-I transformed cells with endothelial cells induces the production of functional matrix metalloproteinase by endothelial cells and results in the degradation of subendothelial basement membrane, allowing extravasation of transformed lymphocytes between endothelial cells (Bazarbachi et al., 2004). These results provide the rationale for a new therapeutic approach based on the inhibition of angiogenesis and on the modulation of adhesion or communication, such as use of kinase inhibitors. Preliminary results in vitro showed that angiogenesis inhibitors, such as monoclonal antibodies anti-VEGF (bevasizumab) or specific kinase inhibitors of the VEGF receptors (PTK-787), inhibit ATL-induced angiogenesis and ATL cell invasion through an endothelial barrier.

References
at the centrosome. Oncogene. 2008; 27:1665-76.


Therapeutic Choices in Patients with Ph-Positive CML: SCT or TKI?

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Abstract

Background: CML is a hematopoietic stem cell disorder which constitutes a clinical model for molecular detection and therapy as characterized by the reciprocal translocation t(9;22) resulting in Bcr/Abl oncogenic fusion gene or the Philadelphia chromosome (Ph) which is expressed as a fusion protein with deregulated tyrosine kinase activity that has been recognized to play a key role in the pathogenesis of the disease. The only proven curative therapy for CML is allogeneic stem cell transplantation (allo-SCT); however, this approach is available for only less than 40% of patients who have an HLA matched donor.

The introduction of imatinib mesylate (IM) in 1998 has revolutionized the management of CML. The drug is a potent and selective tyrosine kinase inhibitor which acts by occupying the ATP-binding site of the ABL tyrosine kinase component of the BCR-ABL oncoprotein and maintains it in an inactive conformation. It offers excellent short-term results, but without long-term follow-up 4.

However this line of treatment requires tremendous resources and it becomes increasingly difficult for hematologists practicing in the developing world to reconcile the difference between what is possible and what is available.

Aim: We retrospectively reviewed the different treatment options that were offered to our CML patients during the last decade.

Patients and methods: A total of 377 patients with Ph-positive CML in first chronic phase were followed during the past 11 years in Nasser Institute hospital for research and treatment and in the National Cancer Institute, NCI, Cairo university.

Among them, 268 were given myeloablative allogeneic SCT, 18 were given a reduced –intensity transplant and 91 patients received imatinib as frontline treatment.

For the allogeneic transplant group, different conditioning regimens were used, 117 patients received fractionated total body irradiation 250 cGy for 4 days (D-7 to D-4) and cyclophosphamide 60 mg/kg for 2 days (D-3 and D-2), (TBI/Cy protocol) during the period between May 1997 to March 2003, 71 patients received busulphan 4 mg/kg for 4 days (D-7 to D-4) and cyclophosphamide 60 mg/kg/day for 2 days (D-3 and D-2), (classical Bu /Cy ) during the period between September 1998 to November 2005, 18 patients received reduced intensity regimen as fludarabine 30 mg/m2 for 3 days (D-4 to D-2) and total body irradiation 200 cGy (D-1), (Flu /TBI protocol) during the period between February 2001 to March 2003. And 47 patients received spaced and fractionated Bu /Cy protocol as busulphan 4 mg/kg/day for 4 days (D-11 to D-8) and cyclophosphamide 30 mg/kg/day for 4 days (D-5 to D-2) during the period between August 2005 to April 2007, and 34 patients received fludarabine 30 mg/m2 for 5 days (D-10,9 and D-4,3,2) and busulphan 4 mg/ m2 for 4 days (D-8 to D-5), (Flu /Bu protocol) during the period between August 2006 to November 2008.

Results

TBI / Cy group

117 patients with chronic phase Ph-positive CML underwent an allogeneic SCT from HLA matched sibling donor during the period between May 1997 and March 2003. Their median age was 29 (range 8-48 y), 62 patients (52 %) were in the first year of diagnosis at onset of transplant.

AGVHD (Grade II-IV) occurred in 43 patients (36%). Limited cGVHD occurred in 20 patients (17%) while extensive cGVHD occurred in 23 patients (19%). After a median follow-up of 9 years and 5 months (113 months), DFS and OS were 30% and 34% respectively. (Fig. 1)

Classic Bu / Cy group

71 patients with chronic phase Ph-positive CML underwent an allogeneic SCT from HLA matched sibling donor during the period between September 1998 and November 2005. Their median age was 29 (range 3-47 y), 30 patients (42%) were in the first year of diagnosis at onset of transplant.

AGVHD (Grade II-IV) occurred in 20 patients (28%). Limited cGVHD occurred in 3 patients (4%) while extensive cGVHD occurred in 12 patients (17%). After a median follow-up of 4 years and 5 months (53 months), DFS and OS were 31%. (Fig. 2)
Reduced – intensity group
18 patients with chronic phase Ph-positive CML underwent an allogeneic SCT from HLA matched sibling donor during the period between February 2001 and March 2003. Their median age was 32 (range 13-49 y). None of the patients developed AGVHD. Limited cGVHD occurred in 2 patients (11%) while extensive cGVHD occurred in 12 patients (17%). After a median follow-up of 7 years and 6 months (90 months), DFS and OS were 25% and 50% respectively. (Fig. 3)

Bu / Cy (spaced and fractionated) group
47 patients with chronic phase Ph-positive CML underwent an allogeneic SCT from HLA matched sibling donor during the period between August 2005 and April 2007. Their median age was 28 (range 6-45 y), 18 patients (39%) were in the first year of diagnosis at onset of transplant.
AGVHD (Grade II-IV) occurred in 10 patients (21%). Limited cGVHD occurred in 7 patients (15%) while extensive cGVHD occurred in 8 patients (17%). After a median follow-up of 3 years (36 months), DFS and OS were 58%. However when we stratified our patients according to onset from diagnosis until transplant, patients with less than one year had a superior outcome with a DFS and OS of 66% compared to only 53% for patients with more than one year of diagnosis (P=0.2). (Fig. 4)

Flu / bu group
34 patients with chronic phase Ph-positive CML underwent an allogeneic SCT from HLA matched sibling donor during the period between August 2006 and November 2008. Their median age was 29 (range 18-47 y), 13 patients (38%) were in the first year of diagnosis at onset of transplant.
AGVHD (Grade II-IV) occurred in 8 patients (23%). Limited cGVHD occurred in 2 patients (5%), extensive cGVHD occurred in 2 patients (5%). After a median follow-up of 2 years (24 months), DFS and OS were 70%. However when our patients were stratified according to onset from diagnosis until transplant, patients with less than one year had a superior outcome with a DFS and OS of 76% compared to only 66% for patients with more than one year of diagnosis (P=0.4). (Fig. 5)

Frontline imatinib group
91 chronic phase CML patients treated with a daily oral dose of IM 400 mg during the period between March 2004 and January 2008 were evaluated after a median follow-up period of 21 months (range 4-60 months).

At 12 months of therapy 68/91 (74%) patients achieved a major cytogenetic response (MCR) from whom 53 patients (53/91, 58%) were in complete cytogenetic response (CCR). At 18 months, 85 patients were evaluated for molecular responses. Fifty one patient (51/85, 60%) achieved a major molecular response (MMR); 38 patients (45%) at 12 months in addition to 13 patients (15%) at 18 months. Bcr-Abl transcripts become undetectable in 22/85 patients (26%) at 24 months follow-up on consecutive measurements. Primary resistance was observed in 16/91 (17%) patients. A suboptimal response was observed in 18/91 patients (18%). All patients with primary resistance (16/16, 100%) and 16/18 (89%) of suboptimal responders failed to achieve 2 log reductions at 6 months versus 3/57 (5%) only in the optimal responder group (p=0.0001). Bcr-Abl kinase domain mutations were performed by allele specific oligonucleotide primers polymerase chain reaction (ASO PCR) in 15 patients (10 suboptimal responders and 5 primary resistance) and was positive in 9/15 (60%) patients. M351T was positive in 4/15 patients (27%) and Q252 was positive in 3 patients (20%). F359V and Y253F were positive in one patient each. T315I was negative in all 15 patients tested. Five patients developed acute blastic crisis (ABC) during treatment (5/91, 5%) with rising Bcr-Abl/Ab ratios (Fig. 6). All failed to achieve 2 log reductions at 6 months of IM therapy. Three tested patients out of five ABC were positive for p loop mutations (two patients Q252H and one Y253F).

Cost considerations
The discovery of imatinib has changed the therapeutic algorithm for CML and is now the therapy of choice for newly diagnosed patients with marked impact on the use of allogeneic SCT in CML. In developing countries the impact has not been so marked, probably because of the cost of TKI. Median cost of each allograft was US$15000, an amount that is enough to cover 6 months of treatment with imatinib (400 mg/day). So, as most of our patient can not afford continuing treatment with TKI especially in view of the lack of a third party payer, allografting still has a relevant role when resources are limited.

Summary and conclusions
Treatment modality for CML patients has changed over the past decade from the standard allogeneic SCT as the only proven curative potential to the use of TKIs, mainly imatinib as frontline treatment. However cost considerations especially in developing countries favor allogeneic transplant as a «once only» procedure compared to a lifelong treatment with an expensive drug that has an excessive burden on resources. Despite inferior results of early transplants, and excellent initial outcome of patients receiving imatinib, it should be noted that outcome of allogeneic transplant has also improved over years which gives a rational approach to young patients with an HLA matched sibling donor who can not afford the cost of imatinib.

References
Figures

Fig 1.

Fig 2.

Fig 3.

Fig 4.

Fig 5.

Fig 6. Frontline Imatinib group (March 2004 – January 2008) No. = 91
The impressive response rates and the good tolerability allowed imatinib to become the golden standard frontline therapy for all CML patients in early chronic-phase. This conclusion has been mainly reached through the results of the IRIS trial. In fact, as shown in a recently presented revision of the data of this study, in the trial-arm in which the patients were assigned to receive imatinib 400 daily, after 7 years of follow-up 60% of patients are still on treatment and almost all of them in stable complete cytogenetic remission (CCyR). The remaining patients (40%) discontinued treatment because of inadequate response, loss of response, adverse events or protocol violation. All together, the overall survivors (OS) after 7 years are 88%, and only 5% of patients had died due to CML-related causes. These data have been deduced so far from a single study and await definitive confirmation from other important ongoing trials, but there is a general consensus about the optimal outcome of more than two thirds of the CML cases treated with standard dose imatinib (400 mg daily).

Criteria to establish failure and suboptimal responses to imatinib have been defined. In particular, hematologic resistance (rare, 2–3% of all cases) at 3–6 months, lack of any degree of cytogenetic response at 6 months, lack of a major cytogenetic response at 12 months (>35% Ph-positive metaphases) and absence of a complete cytogenetic response at 18 months, are all considered failures and other treatment strategies are justified in these cases as the residual probability of achieving optimal response in such patients are scarce. Primary failure occurs in approximately 15% of all patients, but in the “failure” group we must also include those patients (14% in the IRIS) who initially achieve the responses expected at the established time-points, but subsequently lose them. In some of these cases (6–7%) progression to accelerated or blast phase of CML is observed. Failure must be distinguished from what has been defined “suboptimal response”, an intermediate situation between optimal response and failure, in which the response is slower than expected, but there is still a substantial chance for the patient to achieve the awaited response at a later time point. Revision of these guidelines will probably be published in 2009, and probably they will contain more stringent criteria in optimal response definition, as now second generation TKIs are registered and available for suboptimal responders and failure patients. In some cases, suboptimal responses and also failures may simply be due to a too low imatinib plasma level, than may be explained by e.g. poor compliance to daily oral therapy, drug–drug interactions, food interaction or concomitant diseases. In other cases, genetic polymorphisms of the genes involved in the cellular drug influx–efflux processes may be responsible for insufficient (too low) imatinib concentrations within the cells. It has been recently described a correlation of imatinib trough plasma concentrations (Cmin) with clinical responses, event-free survival (EFS), and adverse events (AEs) using 5-year follow-up data from the IRIS study patients randomized to first-line imatinib. The cumulative estimated complete cytogenetic response (CCyR) and major molecular response (MMR) rates were shown to be different between the quartile categories of imatinib trough levels. Patients with a high imatinib exposure showed better CCyR and MMR rates and EFS. An exploratory analysis has shown that trough levels of imatinib were predictive of higher CCyR independently of Sokal risk group. Patient demographics including age, gender, and body weight or body surface area have little impact on imatinib pharmacokinetic (PK) exposure compared with inter-patient variability. Maintaining plasma trough levels at or above the mean population concentration of approximately 1000 ng/mL may be important for achieving improved CCyR and MMR rates. Treatment guidelines have also suggested imatinib dose escalation based on clinical assessments of disease response. Recently, response and survival data were analyzed in a cohort of patients with newly diagnosed CML-CP enrolled on the IRIS trial, who began treatment with imatinib 400 mg daily and subsequently underwent dose escalation to either 600 or 800 mg daily. Reasons for dose escalation were evaluated retrospectively based on two sets of criteria: the IRIS protocol-defined criteria and European LeukemiaNet (ELN) recommendations. Among all 106 patients who underwent dose escalation, freedom from progression to accelerated or blast phase and overall survival were 89% and 84% at 3 years after dose increase, respectively. This analysis supports imatinib dose escalation as an appropriate initial option for patients with CML-CP who do not achieve clinical response milestones or whose disease appears to be progressing. A higher dose of imatinib (800 mg per day) has been suggested to accelerate to achievement and to improve the rates of the cytogenetic and molecular responses. If High Dose Imatinib is really beneficial for all CML patients in early chronic phase or at least for some specific risk subgroup of patients is still matter of investigation and important answers on this topic will soon become available.

However, despite all the efforts to optimize therapy with imatinib, cases of real resistance exist. The most common mechanisms of resistance to imatinib include: (i) BCR-ABL kinase domain mutations; (ii) BCR-ABL overexpression; (iii) clonal evolution with activation of additional transformation pathways.
The most studied mechanism of resistance to imatinib therapy is the development of point mutations within the kinase domain of BCR–ABL. The frequency of BCR–ABL mutations in imatinib resistant patients ranges from 40–90% depending on the CML phase and on the methodology for the detection. Depending on the region where they are located, mutations can actually act by interrupting critical contact points between the drug and BCR/ABL protein or by inducing a conformational change to which imatinib is unable to bind. At present, more than 100 different BCR/ABL mutations have been identified in patients with imatinib-resistant CML. Many of these are relatively rare, whereas the most common, which account for 60–70% of all the mutations, affect residues Gly250, Tyr253, Glu255, Thr315, Met351 and Phe359. Mutations also differ from each other for the kind of resistance they can determine: some mutant clones are completely resistant (Y253F/H, E255K, T315I), others only partially (M244V, F317L, Met351T). In the latter case, the sensitivity can be restored by simply increasing the imatinib dose. The mutations with a greater level of resistance fall inside the ATP binding site of the KD domain, an highly conserved region responsible for phosphate binding and known as phosphate-binding loop (P-loop) (a.a. 248-256).

For the imatinib resistant and intolerant cases, second generation powerful tyrosine kinase inhibitors (TKIs) have been developed and registered. For the imatinib resistant and intolerant cases, second generation powerful tyrosine kinase inhibitors (TKIs) have been developed and registered. Dasatinib (Sprycel, Bristol-Myers Squibb, New York, NY), a multi-kinase inhibitor with an in vitro potency against unmutated BCR-ABL 325 times greater than imatinib, inhibits most known BCR-ABL mutants with the exception of T315I. Dasatinib also inhibits other tyrosine kinases, including the Src Family Kinases (SFK). The SFK, such as Lyn, may play an important role in the development of resistance to imatinib. Orally administered dasatinib has shown consistent clinical benefit in patients with CML-CP, CML in accelerated phase (CML-AP), CML-BP or Ph+ acute lymphoblastic leukemia (Ph+ALL) resistant or intolerant to imatinib and is approved for use at a dosing regimen of 70 mg twice daily. A Phase 3 dose-optimization study in patients with imatinib-resistant or -intolerant CML-CP demonstrated that dasatinib 100 mg once daily had similar efficacy and improved tolerability relative to 70 mg twice daily, 23 and as a result, the recommended initial dasatinib dose for these patients is currently 100 mg once daily. For instance, the fact that dasatinib acts potently on many members of the SFKs and also on KIT, PDGFR and Ephrin Receptor (EPHA2) tyrosine kinases, which are directly implicated in many biological processes, may provide the physiological explanation for some of the toxicities observed such as pleural effusion and myelosuppression.

Nilotinib (Tasigna®, Novartis Pharmaceuticals, East Hanover, NJ, USA) is a second-generation tyrosine kinase inhibitor (TKI) designed with enhanced selectivity and potency for BCR-ABL compared to that of imatinib. In vitro studies demonstrate that nilotinib is 20-to 50-fold more potent than imatinib. Nilotinib exhibits in vitro inhibitory activity against the majority of mutant BCR-ABL kinases that may be present following imatinib resistance, with the exception of the T315I mutation. Nilotinib is approved for the treatment of patients with Ph+ CML-CP and accelerated phase (CML-AP) resistant to or intolerant of prior therapy, including imatinib. The approval of nilotinib in CML-CP and CML-AP was based on the results of a pivotal phase II registration trial which demonstrated significant efficacy and tolerability in these patients. Nilotinib treatment is generally very well tolerated and the associated toxic effect may include myelosuppression, skin rashes, and biochemical abnormalities as lipase, transaminase and bilirubin elevations. Also hyperglycemia is commonly observed, particularly in patients with latent or overt diabetes. However, the cases of clinically relevant pancreatic and liver toxicities are really sporadic. Also effects on QT prolongation were minimal and of no clinical relevance.

Finally, to overcome imatinib resistance and to further improve the percentage of good responders, two different strategies can presently be envisaged. The first is to treat more intensively patients already at diagnosis, in order to accelerate responses and to hamper resistance to develop. The second is to react as soon as possible when signs of a lower degree of sensitivity to imatinib therapy become evident, like a slower clearance of the BCR/ABL transcripts in the peripheral blood verified by RQ PCR. The first strategy can be accomplished by increasing imatinib dosage to 800 mg daily or by using already as frontline therapy the more powerful second generation TKIs, like dasatinib and nilotinib, that have already been demonstrated to be highly effective as second line therapy in (and are approved for) imatinib resistant cases and show an acceptable degree of toxicity. This strategy is presently being investigated in several ongoing clinical protocols designed for all or for specific groups of patients, like the ‘Sokal’s high’ cases. The first data derived from these studies, still very preliminary, seem encouraging in terms of CCyR and major molecular remission rates, but the risk may be to overtreat the majority of the patients who can respond optimally also to imatinib 400 mg daily, with all the related problems in terms of short-term and long-term effects, that in the case of the new TKIs nobody knows exactly. Finally, from a theoretical point of view, if resistance is not an ongoing process, but rather a pre-established characteristic of some Ph-positive cells already present at diagnosis, the real advantage in terms of final outcome with respect to the traditional sequential therapy with imatinib as first line therapy and a second generation TKI as second line therapy awaits to be verified. By contrast, the major risk of the second strategy derives from the fact that it has recently been demonstrated that compound mutants (2 or 3 BCR-ABL mutations in the same molecule) may arise by using sequentially different TKIs. This finding outlines the potential hazards of sequential kinase inhibitor therapy to overcome resistance and suggest a role for a combination therapy with different ABL kinase inhibitors in the same therapeutic scheme, used sequentially or simultaneously. Trials aiming to test the possible benefit of “combination therapies with TKIs” are planned.
Acute leukemia (AL) is a disease characterized by abnormal proliferation of primitive hematopoietic cells outcrowning normal marrow elements. When first described it was inevitably fatal within a very short period. The marked progress in the field of chemotherapy and other therapeutic modalities has changed the outcome of acute leukemia, at least in some subtypes, from a fatal to a potentially curable disease. This was associated with trials to classify acute leukemia into different subtypes looking for proper diagnosis which would determine the line of therapy. Expressions like species specific and personalized therapy have been introduced. Species specific therapy involves broad classification into subtypes while personalized therapy requires in depth characterization of the malignant cells at the individual case level. Such an approach requires initially an accurate diagnosis and requires, as well, defining disease marker(s) that would predict response to therapy upfront or during the course of treatment.

**Diagnostic and prognostic workup**

After clinical examination, the first task is to confirm the diagnosis and make a proper classification of the type of leukemia. The second task is to look for prognostic markers that would help determining the proper therapeutic regimen. The third task is to follow up the patient for response and probably change the treatment plan.

A diagnostic workup starts basically with a full blood count, a bone marrow (BM) aspirate and cytochemistry. Samples are taken, as well, for immunophenotyping, cytogenetics and molecular genetics.

**Morphology and Cytochemistry**

Examination of peripheral blood (PB) and BM smears gives the first clue to diagnosis. BM is essential to fulfill the criterion of ≥20% blast to establish the diagnosis of acute leukemia (AL) (1, 2). The morphology of the blast cells, though not sufficient in most cases, is still a corner stone in diagnosis. The presence of Auer rods would exclude acute lymphoblastic leukemia (ALL). Certain types of acute myeloid leukemia (ANLL) have characteristic morphology namely monocyte leukemia (M4 and M5), the classical hypergranular form of acute promyelocytic leukemia (M3), and most cases of erythroid leukemia (M6). Acute megakaryoblastic leukemia (M7) cannot be diagnosed but may be suspected from morphology. The next step in the diagnostic workup is cytochemistry which is the main tool to classify AL into its two main categories, ALL and ANLL. A positive staining of the blast cells for myeloperoxidase (MPO), chloracetate esterase and/or Sudan Black would confirm a diagnosis of ANLL. A negative staining however would not exclude such a diagnosis. It is worth mentioning that a common mistake is done at this stage by reporting the case as ALL on account of negative cytochemistry. The case can still be an M0 which is by definition lacking Auer rods and negative for all myeloid specific cytochemical stains (1, 2). This subtype can only be diagnosed by immunophenotyping (IPT) as will be mentioned later. Cytochemistry can further establish the FAB subtype. M3 is associated with very strong MPO which will also stain the Fagots. It is especially important in the diagnosis of the hypogranular variant which could be morphologically misinterpreted as M5. Cytochemistry is the main diagnostic tool in monocytic leukemia where M5 shows strong staining for nonspecific esterase that is completely inhibited by fluoride while the myeloid elements in M4 show weak staining that is not inhibited by fluoride. Dual esterase for monocytic and myeloid elements on the same smear is preferred in cases of M4 for accurate determination of the relative percentage of each component. Periodic acid Schiff (PAS) staining is the diagnostic tool in M6 with its characteristic block positivity. Acid phosphatase (AP) is of limited value except in case of TALL where it shows its characteristic paranuclear dot like positivity in the place of Golgi apparatus. Though not diagnostic, AP has a characteristic pattern in M7 with strong dot like positivity distributed all over the cell. With a negative cytochemistry ALL may be highly suspected but not definitely diagnosed. With the exception of AP+ TALL, ALL is an exclusion diagnosis that has to be confirmed by immunophenotyping. After morphology and cytochemistry, most ANLL cases (except M0 and M7) would have been properly categorized, or at least suspected, according to FAB classification. The other cases are most probably ALL.

**Immunophenotyping**

The next step is to perform immunophenotyping. It is performed using monoclonal antibodies (Mo Abs) and multiple color (3-4 colors) flow cytometry. IPT is a must in ALL; cases have to be classified as TALL, precursor B-ALL or mature B- ALL. Each of these three categories has a different treatment protocol and they vary in prognosis (3, 4). IPT value in ANLL used to be confined to the diagnosis of M0 and M7 by detecting myeloid antigen expression on the cytochemically negative blast cells at the individual case level. Such an approach requires initially an accurate diagnosis and requires, as well, defining disease marker(s) that would predict response to therapy upfront or during the course of treatment.
cells in case of M0 and the megakaryocytic-specific markers (CD41, CD42 and/or CD61) in case of M7. However IPT is currently an integral part of the diagnostic workup of both ALL and ANLL, to be used as a marker for minimal residual disease (MRD) detection. At least two 4-color panels expressed on > 50% of the blast cells at diagnosis have to be specified for each case; this is achievable in > 94% of cases (5). The use of two panels will overcome the possible Immunophenotypic shift that might occur in some cases (6).

The panel of Mo Abs used for ALL should include

- **T Lineage:** cytoplasmic CD3 + CD5, CD2 or CD7. CD4 and CD8 are essential to exclude residual normal T cells; they also indicate the stage of T cell differentiation.
- **B Lineage:** cytoplasmic CD22 + CD19 (pan B), CD10 for CALL, cytoplasmic μ for pre-B as well as κ and λ for mature-B.

For determination of the stage of T cell differentiation, CD1 is added to the panel.

- **Myeloid Markers:** CD13, CD33, MPO to exclude M0 and diagnose biphenotypic leukemia, CD14 for M4 and M5 and CD41/CD42/CD61 for M7
- **Others:** CD45, CD34 and anti class II MHC.
- **Markers for MRD:** TDT, CD66c, NG-2, CD21, CD38 and CD58 (7)

According to marker expression, cases are classified into: (1) precursor-B including Pro B: CD19+, Cy Cyt CD22+, cyt CD79α± and CD10-. CALL: CD10+, Immunoglobulin (Ig)- and Pre B: cyt μ+ and slg-. (2) Mature-B: CD19+, CD22+, cyt CD79α± and CD10+, slg κ or λ +. (3) TALL: CD3 + CD5, CD2 and/or CD7.

Flow cytometry is also useful to measure the DNA index. An index of ≥ 1.16 < 1.6 is a good prognostic parameter; the good prognosis has been attributed to double trisomy of chromosome 4 and 10 which has to be looked for by FISH technique in any case with DNA index > 1 (8)

**Cytogenetics**

Conventional Karyotyping is essential for all cases. The tremendous progress in molecular genetics did not undermine its role in the workup of acute leukemia. It gives an overview of the findings including multiple and complex translocations. It is also the first step in the discovery of any possible new genes. Marked progress in the techniques used from simple G-banding to FISH, to whole chromosomal staining, spectral karyotyping (Sky) technique and comparative genomic hybridization has added more to its value. Karyotyping can detect both numerical and structural abnormalities. However there is a number of translocations that are cryptic and cannot be detected by conventional karyotyping e.g. t(12;21). Others may be missed in certain cases by Karyotyping and detected only by molecular techniques e.g. t(9;22). In other situations, still, the translocation has to be confirmed at the molecular level for targeted therapy e.g. t(15;17) (PML, RARA) for all-trans-Retinoic Acid (ATRA) therapy.

**Molecular Genetics of ALL**

**Molecular genetics of Precursor-B ALL**

About 30-35% of ALL cases show one or the other of four common translocations. The t(12;21)(p13;q22) ETV6/RUNX1a “cryptic” chromosome rearrangement is associated with favorable prognosis using treatment protocols for low risks ALL (9). The t(1;19)(q23;p13) TCF3/PBX1 fusion gene is usually associated with cyt μ positive precursor B ALL (pre-B ALL). This translocation has been associated with a poor response to antimitabotile therapies and an unfavorable outcome in the past. Recent treatment protocols for higher risk ALL have significantly improved the long term disease free survival rate (10). The t(9;22)(q32;q11) BCR/ABL, or Philadelphia (Ph) chromosome is usually detected at the cytogenetic level. However molecular analysis to detect BCR/ABL1 fusion mRNA product identifies additional cases that are missed by conventional karyotyping and either p210 or p190 might be detected. The prognosis is unfavorable in both children and adults (11). The last group of chromosomal translocations with a known prognostic significance is the rearrangement of chromosome 11q23; t(4;11)(q21;q23) MLL/AF4 is the most common among this subgroup accounting for 60-70% of these cases. This translocation is associated with poor prognosis (12).

**Molecular genetics of TALL**

These may be classified into three groups (13).

**I- Fusion transcript:**

- CALM-AF10: It has an incidence of 10% in both children and adults
- SIL-TAL1: It has an incidence of 5-10% in children and 25% in adults

The clinical relevance of both is still controversial with claimed good prognosis in children

**II- Translocations:**

- TLX1 (HOX11): It has an incidence of 5-10% in children and 15-20% in adults. It is claimed to be associated with poor prognosis though it is still controversial.
- TLX3 (HOX11L2): It has an incidence of 25% in children and 5-10% in adults. It is associated with good prognosis both in children and adults
- MYB: It has an incidence of 5-10% in both children and adults.
- LMO1 and LMO2: Its incidence is about 45% (including deletions)

**III- Point mutations/deletions:**

- NOTCH1: It has an incidence of 50% in both children and adults. Its prognostic impact is controversial.
- FBW7: It has an incidence of 25-30% in both children and adults.
- CDKN2A deletions: Rare

**Molecular genetics of ANLL**

At the cytogenetic level, ANLL is extremely heterogeneous with > 200 reported structural and numerical aberrations (14). Cytogenetics at diagnosis is amongst the strongest independent prognostic factors (15). However, 40-45% of ANLL have no cytogenetic abnormalities, what is known as cytogenetically normal (CN) ANLL.
Translocations t(8;21) (AML1/ETO) Runx1- RUNX1T1, Inv (16) (CBFB/MYH11) and t(15;17) (PML/RARA) are associated with good prognosis. Conversely, translocations involving band 3q26 (with overexpression of EVI gene or those with complex karyotype are generally associated with inferior outcome (14, 15). The CN-AML group is associated with intermediate prognosis. Recently, however, a prognostic role of molecular genetics within cytogenetically defined groups of ANLL patients is more and more appreciated (16).

Genetic stratification of AML with core-binding factor: t(8;21) & Inv(16)

This group of patients has a favorable prognosis; Still 50% are not cured with contemporary chemotherapy. It was found that the presence of KIT mutations would affect the prognosis in these cases. KIT mutations occur mainly in exon 8 and 17. It has an incidence of 20-45% and claimed to have variable geographical distribution. It is associated with adverse prognosis in the t(8;21) group and a higher incidence of relapse in Inv (16)/(17, 18 ). The other aspect of the coin, however, is that it constitutes a potential therapeutic target for tyrosine kinase inhibitors (TKIs). In a recent study the presence of either KIT, FLT3 internal tandem duplication (ITD) or JAK2 V617F mutations were shown to be associated with bad prognosis in this group of patients (19).

Molecular Markers in Cytogenetically Normal ANNL (CN-ANLL)

About 40% of patients with CN AML leukemia can be cured but until recently this subgroup could not be recognized. A number of prognostic markers can now be used to subcategorize this group of patients. These include gene mutations and overexpression of single genes.

Mutations of the FLT3 gene

Internal tandem duplications (ITDs) of the FLT3 gene occur within the juxtamembrane domain (exon 14 and 15). The duplication can vary in length from 3 to more than 400 nucleotides. FLT3-ITDs are detected in 28-33% of CN ANLL patients (20, 21). Further 5-14% of CN-ANLL patients carry missense mutations in exon 20 of FLT3 i.e. within the activation loop of the tyrosine kinase domain (FLT3-TKD). FLT3-ITD has been found to be an independent prognostic factor associated with shorter complete remission duration (CRD), disease free survival (DFS) and overall survival (OS). There is evidence that the outcome may be related to the level of the mutant allele than just to its mere presence; only patients with loss of wild type FLT3 have dismal outcome and not those with heterozygous mutations (20). The prognostic significance of isolated FLT3-TKD remains controversial.

Mutations of the MLL gene

Partial Tandem Duplication spanning exons 5 through 11 or less frequently 12 occurs in about 8% of adult de novo ANLL. It is associated with shorter remission duration but not OS. Improved outcome has been recently reported in young adults treated with autologous SCT in first remission (22).

Mutations of the CEBPA gene

The CEBPA gene encodes C/EBP α protein. It occurs at a frequency of 15-19% and is associated with longer CRD and OS (23).

Mutations of NPM1 gene

NPM1 encodes nucleophosmin; it occurs at a frequency of 45-64% of CN-AML and is associated with better CR rate, EFS, RFS, and OS. Forty per cent of patients with NPM1 mutations have FLT3-ITD. Its good prognostic impact is effective only in absence of FLT3-ITD; it has no effect in presence of FLT3-ITD (18). NPM1 mutations are associated with a beneficial effect of ATRA given after intensive conventional chemotherapy in elderly patients with non-APL AML. The effect is also confined to the FLT3-ITD negative patients (24, 25, 26).

Mutations of the WT1 gene

It has been suggested that WT1 protein could promote stem cell proliferation and induce a block in differentiation. It occurs at a frequency of 10% in CN-ANLL. Its association with FLT3-ITD is especially detrimental with failure to achieve CR (27).

Mutations in AML1

Other than the t(8;21) (AML1/ETO) Runx1- RUNX1T, mutations of the AML1 have been shown to be involved in other AML subsets. They are found in nearly all cases with trisomy 13, in a large number of cases with trisomy 21, and also in 10% of CN-AML (28). No data is, currently, available on its clinical relevance.

Mutations in NRAS gene

NRAS mutations have not been shown to be of prognostic significance, yet they may provide a target for molecular therapy (29).

Overexpression of BAALC gene

BAALC expression is mostly detected in hematopoietic precursors and neuroectoderm-derived tissues. High expression is encountered in ALL, AML, ABC but not CML. High expression in CN-ANLL is associated with primary resistance, shorter DFS, OS and higher cumulative incidence of relapse (CIR). It is especially predictive in absence of FLT3-ITD & CEBPA mutations (30). It has been suggested that patients with high BAALC expression might benefit from allogeneic SCT (31).

Overexpression of the ERG gene

ERG is one of > 30 members of ETS gene family. In CN-ANLL high ERG expression is associated with adverse impact on CIR and EFS. Its adverse impact on OS is observed only, in patients with low BAALC (32).

Overexpression of MN1 gene

Recently, overexpression of MN1 was found to be associated with shorter OS and RFS in CN-ANLL (33). These results need further confirmation (29).

To evaluate the impact of each individual marker in the concert of all other markers it will be necessary to analyze large cohorts of homogenously treated patients for the various genetic changes (29). In a metaanalysis of 872 younger adults with CN-AML (34), mutations in NPM1, FLT3, CEBPA, MLL and NRAS were analyzed. Two genotypes consistently appeared in multivariate analysis as markers of favorable prognosis associated with good response to therapy, favorable relapse-free survival and overall survival. These are CEBPA mutant associated with 62% 4 year survival and NPM1 mutant/ FLT3-ITD negative associated with 60% 4 year survival. The latter subgroup does not benefit from allogeneic SCT in first line therapy (29).
An algorithm for laboratory diagnostic and prognostic workup of Acute Leukemia

Basic workup
Complete blood picture, bone marrow aspirate (Biopsy may be done in selected cases especially M7), cytochemistry as indicated, immunophenotyping and conventional karyotyping. Cases will be categorized into ALL and AML with proper FAB classification for AML and immunophenotype for ALL. Further molecular testing depends on the subtype.

Precursor B ALL
- RT-PCR for t(12;21); t(1;19); t(9;22) (both p190 and p210)
- FISH for MLL gene rearrangement.

TALL
- HOX11, HOX11L2 and SIL-TALL expression.

AML
All cases should be tested for t(8;21), Inv (16) and t(15;17).
- AML with core-binding factor [t(8;21) and Inv (16):]
  - FLT3-ITD.
  - KIT mutations
  - JAK2-V617F mutation

- Cytogetenically normal AML (CN-AML):
  - Test for FLT3-ITD, CEBPA, MLL and WT1 mutations in all cases.
  - Test for NPM1 mutations and BAALC expression in FLT3-ITD negative patients.
  - Test for ERG expression in BAALC low patients.

References


Small Cell Lung Cancer

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Although Small Cell Lung Cancer (SCLC) represents a smaller proportion of all lung cancers than it did 20 years ago, it remains a common cause of mortality that requires more basic and clinical research than is currently underway. Treatment paradigms have changed little since the 80’s. Despite a generally spectacular initial responsiveness to chemotherapy and radiotherapy, the vast majority of patients with SCLC will still relapse and eventually die within 12 to 18 months.

An accurate staging is essential to determine the treatment program since the approach must be curative in case of limited disease (ie those patients whose the whole disease can be included in one radiotherapy volume) and palliative in case of extensive disease (ie all those patients whose disease cannot be included in one radiotherapy volume). Practically, is defined limited a tumour limited to one hemithorax, with ipsilateral or contralateral regional (interbronchial and mediastinal) lymphnodes but without pleural effusion or distant metastases. A whole body CT scan, a bone scan and a bone marrow biopsy constitute the standard assessment of SCLC. PET scan and brain MRI are now probably the most accurate way to stage the patient. Standard biology, LDH and tumour markers such as CEA and NSE are also part of the initial work-up.

The combination of etoposide and cisplatin (or carboplatin) is the traditional first line treatment for almost all patients. The sequential or concurrent addition of adriamycin, and cyclophosphamide slightly improves the results but with a substantially higher toxicity. A Japanese study suggesting the superiority of irinotecan over etoposide could not be confirmed in several western randomised trials. The addition of Growth Factor Receptor Inhibitors, Signaling Inhibitors, Antibodies against Adhesion Molecules, Apoptosis promoters, Angiogenesis Inhibitors or vaccines all failed up to now at substantially improving survival of SCLC.

In patients with limited disease, the addition of radiotherapy to chemotherapy may increase the rate of complete responses up to 70% and the probability of long term survival from 5-7% to 15-20%. Early concurrent associations appear offering the best chance of positive outcome.

Second line treatments are rarely successful and survival duration largely depends of the disease-free interval. If the progression occurs at least 6 months after initial treatment discontinuation, it is generally recommended to resume the initial etoposide-cisplatin combination. If the relapse occurs earlier, the standard second line agent is Topotecan. Amrubicin has recently showed some promising results that should be confirmed in a randomised study.

Finally, prophylactic cranial irradiation has been largely evaluated due to the high rate of brain metastases in SCLC. All studies confirm the benefit of its use in patients responding to chemotherapy.
Advances in Radiotherapy Techniques in NSCLC

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Radiation therapy plays a crucial role in the management of lung cancer. However, with two-dimensional (2-D) radiotherapy planning, the local control was poor and dose escalation was associated with increased toxicity, particularly when concurrent chemotherapy was given.

Three-dimensional (3-D) conformal radiotherapy (3-D CRT) might improve local control and possibly survival compared with 2-D therapy in stage I non small cell lung cancer (NSCLC).

In addition, dose-escalation phase I/II clinical studies have shown promising clinical outcomes in stage III NSCLC, with improvements in survival and toxicity, with the use of 3-D CRT, although a phase III study is needed to confirm the results. The three main reasons for local failure after radiotherapy are (1) geographic misses due to inadequacy of imaging tools for staging and radiotherapy planning; (2) geographic misses due to respiratory tumor motion during radiation delivery; and (3) inadequate radiation dose because of the potential for significant toxicity. Image-guided radiotherapy (IGRT), particularly radiotherapy planning based on positron emission tomography/computed tomography (PET/CT), consideration of individualized tumor motion with four-dimensional (4-D) CT, and on-board imaging-guided adapted radiotherapy during the course of treatment may allow more accurate tumor targeting and reduce side effects. IGRT with radiation dose escalation or acceleration could significantly improve clinical outcomes for patients with lung cancer. For example, image-guided stereotactic body radiotherapy (SBRT) has been shown in phase II clinical trials to improve local control and survival in early-stage NSCLC compared with historical data, and intensity-modulated radiotherapy (IMRT) may be better tolerated than 3-D CRT. As information about IGRT for lung cancer continues to emerge, standard radiotherapy approaches for patients with NSCLC are evolving. Guidelines and step-by-step techniques for the use of IGRT in mobile lung cancers are needed to implement IGRT into daily clinical practice. Recent developments in image-guided radiotherapy are ushering in a new era of radiotherapy for lung cancer. Positron emission tomography/computed tomography (PET/CT) has been shown to improve targeting accuracy in 25 to 50% of cases, and four-dimensional CT scanning helps to individualize radiotherapy by accounting for tumor motion. Daily on-board imaging reduces treatment set-up uncertainty and provides information about daily organ motion and variations in anatomy.

Image-guided stereotactic radiotherapy can achieve local control rates exceeding 90% through the use of focused, hypofractionated, highly biologically effective doses. These novel approaches were considered experimental just a few years ago, but accumulating evidence of their potential for significantly improving clinical outcomes is leading to their inclusion in standard treatments for lung cancer at major cancer centers.

Image-Guided Target Volume Delineation

Gross Tumor Volume

The pulmonary extent of lung tumors should be delineated on pulmonary windows and level settings in CT images, and the mediastinal extent of tumors should be delineated using mediastinal windows and level settings. In general, a lymph node larger than 1 cm in its shortest dimension on CT is considered positive, because the risk of involvement is more than 15%. Functional imaging such as (FDG)-PET is quite important for disease staging and radiation treatment volume delineation in NSCLC, particularly in stage III disease. In particular, FDG-PET can help to categorize suspected mediastinal and hilar lymph node adenopathy and distinguish benign collapsed lung tissue from tumor. Currently, a standard uptake value (SUV) equal to or higher than 2.5 is suggested as a threshold. However, the SUV is determined not only by the presence of cancer but also by the size of the lesion, presence of inflammation, timing of imaging after injection of 18F-FDG, blood glucose level, etc. FDG-PET scanning usually can only detect cancer lesions larger than 5 to 10 mm. For smaller lesions, clinical judgment should be applied. Inflammation can cause false positive findings on FDG-PET scans, and biopsy is recommended in the event of questionable findings. Pre- and post treatment SUVs of FDG-PET were found to be predictive of survival in NSCLC. Recent clinical data have also shown that in NSCLC treated with standard concurrent chemoradiotherapy, an SUV higher than 13.8 was associated with a local recurrence rate of 65.5% compared with a rate of less than 25% in lesions with an SUV less than 13.8.

Tumor Motion Consideration

A major obstacle to radiotherapy target delineation has been respiration-induced target motion (also known as intrafractional tumor motion), which can add
considerable geometrical uncertainty to the radiation treatment. Such motion requires enlargement of the treatment field portals to cover the movement of the tumor during treatment. The development of 4-D CT with multislice detectors and faster imaging reconstruction has facilitated the ability to obtain images while patients breathe and to assess organ motion. 4-D CT involves acquiring over-sampled CT information and correlating these data with information about the respiratory cycle.

4-D CT-Based ITV

When 4-D CT is available for treatment planning, the use of a new concept called internal gross tumor volume IGTV, which is the envelope of the GTV throughout its motion during respiration. Delineating the IGTV from 4-D CT images involves outlining the tumor volume on the expiratory phase of the 4-D images and registering the outline on other phases of the images to create a union of target contours enclosing all possible positions of the target. Another method is to create an image of maximum intensity projection by combining data from the multiple CT data sets with data from the whole-breath cycle and modify tumor volume by visual verification of the target volume. In this case, the ITV should consist of the IGTV plus a margin to account for microscopic disease (8 mm). Even with 4-D CT, the free-breathing simulation is only a snapshot and a single stochastic sampling of the patient’s breathing.

Attention should be paid to irregular breathing and variations in the patient’s breathing pattern over the course of each treatment session and the entire treatment course and to the effects of these irregularities on the ITV margin.

Image-Guided Stereotactic Body Radiotherapy

The conventional radiotherapy dose (60–66 Gy) for patients with early-stage NSCLC is associated with a local recurrence rate of more than 50%. Phase II clinical studies have shown that hypofractionated SBRT provides promising local control rates (more than 85%) and survival rates with minimal toxicity in patients with stage I (T1–2 N0 M0) or select stage II (T3 N0 M0) NSCLC because of higher biologically effective dose (BEDs) and more accurate targeting. According to Onishi et al., BEDs of 100 Gy or more are associated with better local control (91.9 Vs. 73.6%) and survival rates (88.4 Vs. 69.4%) than are BEDs of less than 100 Gy. However, the optimal dose regimen for SBRT is controversial. Peripheral lesions can be subjected to higher BEDs, such as 60 Gy in three fractions developed by Dr. Timmerman’ group (current RTOG phase II clinical trial regimen), but treatment of centrally located lesions with such a high-BED regimen can be associated with considerable long-term toxicity. Because of the significantly higher fraction size used in SBRT, IGRT is crucial for optimal target coverage and sparing of normal structures.

Image-Guided Intensity-Modulated Radiation Therapy

The use of IMRT for lung cancer has been delayed because of concerns that it may deliver low, yet damaging, doses to larger volumes of normal lung tissue than does conventional 3-D CRT. Moreover, tumor movement due to respiration introduces another level of complexity to both the IMRT dosimetry and the technique used. Virtual clinical studies were conducted to compare IMRT with 3-D CRT with respect to target dose, tumor conformity, and normal tissue sparing in patients with early stage and locally advanced NSCLC. IMRT may be more suitable than 3-D CRT treatment planning for patients with advanced-stage disease with large GTVs and thus greater volumes of normal lung exposed to irradiation. Using IMRT, the median absolute reduction in the percentage of lung volume irradiated to more than 10 Gy was 7% and that irradiated to more than 20 Gy was 10%. The volumes of the heart and esophagus irradiated to about 50 Gy and the volume of normal thoracic tissue irradiated to more than 10 to 40 Gy were also reduced using the IMRT plans. A marginal increase was noted in the lung volume exposed to more than 5 Gy (V5) in the IMRT plans in half of the patients. V5 was found to be correlated with lung toxicity. To reduce the potential for delivering low doses less than 10 Gy to normal lung and to reduce beam delivery time, the use of fewer beam 5–7 beams is suggested. Although IMRT may be effective in reducing normal tissue toxicity and improving tumor coverage, its high dose gradient and conformity require high levels of precision in dose delivery and tumor localization. The complexity introduced by tumor motion must also be recognized when using IMRT, and 4-D CT planning is recommended. Unlike 3-D CRT, IMRT treats only a portion of the target volume at a particular time. A great deal of concern has been expressed as to whether target motion and collimator motion during IMRT delivery have substantial interplay, thus degrading the planned dose distributions. For IMRT to be feasible and more effective in treating NSCLC, motion-reduction techniques such as breath-holding and tumor tracking should be explored further. Preliminary clinical studies indicate that IMRT may reduce toxic effects in normal tissue in selected patients, particularly for those with tumors that movement can be controlled to be less than 5 mm, such as in the case of a superior sulcus tumor with chest wall/vertebral body involvement, and may allow further dose escalation.
Adjuvant Treatment for Resectable Non-small Cell Lung Cancer (NSCLC)

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Despite optimal surgical management, 5-year survival rate of resected NSCLC ranges between 73% for pathological stage Ia and 25% for pathological stage IIIa.

In the early 90’s, the Medical Research Council and Institut Gustave-Roussy performed a large overview on the role of chemotherapy in NSCLC using updated individual data. A 13% reduction in the risk of death was observed, suggesting an absolute benefit of 5% with adjuvant chemotherapy at 5 years (p=0.08). Sex, performance status, age and histologic subtype had no impact on this effect. These results constituted the rationale for a new generation of randomized studies with platin-based regimens.

A North American Intergroup Trial (Int 0115) demonstrated that a combination of 4 cycles of chemotherapy (etoposide-cisplatin) plus concomitant thoracic radiotherapy was not superior to radiotherapy alone given at the same dose in 463 patients with resected stage II and IIIA NSCLC. Additionally, there was no impact of the p53 and k-ras modifications on the outcome of patients.

In the ALPI trial, patients with resected stage I-IIa NSCLC were randomly allocated to receive either 3 courses of MVP (Mitomycin 8 mg/m² day 1; Vinblastine 3mg/m² day 1 and 8; Cisplatin 100 mg/m² day 1 every 3 weeks for 3 cycles) or no adjuvant treatment after complete resection. Overall 1209 patients were enrolled into the study, 606 in the chemotherapy arm and 603 in the control arm. In the chemotherapy arm, 69% of patients completed the treatment but half of them had treatment modifications. Radiotherapy was delivered in 482 patients. A total of 1088 patients were analysed with a median follow-up of 63 months. H.R. was 0.94 for overall survival and 0.89 for disease-free survival. No statistically significant difference was observed even if the difference was borderline significant for stage II disease.

The IALT was a large worldwide randomized study whose aim was to determine the impact on overall survival of 3 to 4 cycles of a cisplatin-based chemotherapy (CT) regimen after complete surgical resection in patients with stage I-III NSCLC. Thoracic radiotherapy might be given according to the preregistration policy of each centre. There were 932 pts allocated to CT and 67% of patients received at least 300 mg/m² of cisplatin. The drug combined with cisplatin was etoposide (56%), vinorelbine (27%), vinblastine (11%) and vindesine (6%). There were 935 pts in the control arm. After a median follow-up of 56 months, overall survival was significantly different between the 2 arms: 2 and 5-yr survival rates were 70% and 45% in the CT arm vs 67% and 40% in the control arm respectively (HR=0.86 [0.76-0.98], p=0.03). Disease-free survival was also significantly different: 61 % and 39% in the CT arm vs 55% and 34% in the control arm at 2 and 5 yrs respectively (HR=0.83 [0.74-0.94], p=0.003). No significant interaction was observed with age, gender, PS, type of surgery, pStage, histology, cisplatin dose, combined drug, radiotherapy. Nevertheless, the effect was no longer significant at 90 months (HR=0.91 [0.81 to 1.02], p=0.10 due to a higher rate of non-cancer related deaths in the chemotherapy arm. ERCC1 was immunohistochemically evaluated in 761 tumor specimens of patients in the IALT-Bio program. ERCC1 expression was positive in 44% and negative in 56%. A benefit from cisplatin-based adjuvant chemotherapy was associated with the negative expression of ERCC1 (test for interaction, p=0.009).

In the post-operative subgroup of the Big Lung Trial, no benefit from adjuvant chemotherapy was observed among 381 patients but the population was not homogeneous in particular concerning the quality of the resection, and the compliance to chemotherapy was poor.

A Japanese randomized study compared adjuvant UFT for 2 years to no treatment in patients with completely resected stage I NSCLC. Among 979 eligible patients, there was a significant advantage in favor of UFT (p=0.036) but the benefit was restricted to the 27% of patients with T2N0 NSCLC. At the 2004 ASCO meeting, the Japanese adjuvant UFT meta-analysis confirmed a significant advantage of the drug compared to control in 2003 patients (p=<0.001).

The NCI-Canada conducted a phase III trial (JBR 10) comparing surgery alone to surgery followed by adjuvant chemotherapy with cisplatin and vinorelbine in 459 eligible patients with stage Ib and II resected NSCLC. They showed a 15% benefit at 5 years (p=0.012). The benefit was restricted to stage II patients.

The CALGB also conducted a randomized trial in 344 patients with stage Ib NSCLC (CALGB 9633). The initial benefit at 4 years reported with adjuvant Paclitaxel-Carboplatin compared to no adjuvant treatment was not confirmed with a longer follow-up and the benefit is only 3% at 5 years (p=0.10).

In the ANITA 1 trial, which also concerned patients with completely resected NSCLC, chemotherapy consisted of 4 cycles of cisplatin at 100 mg/m² every 4 weeks and 16 cycles of vinorelbine at 30 mg/m² weekly compared to a control...
arm. A total of 831 patients were included from October 1994 to December 2000. There were 35% stage I, 30% stage II and 35% stage III. Again, there was a survival advantage for adjuvant chemotherapy. Survival rates were 68%, 51% and 45% at 2, 5 and 7 years in the chemotherapy arm vs 63%, 43% and 37% respectively. RR was 0.80 [0.66-0.96] with a p value of 0.017.

The LACE meta-analysis reported at ASCO 2006 included a total of 4584 patients accrued in the 5 recent cisplatin-based adjuvant trials. It confirmed the benefit of adjuvant chemotherapy with a 5.3% improvement of survival at 5 years (p=0.0043). Disease-free survival was also improved (5.2% at 5 years, p<0.0001).

Looking at the pathological stage, there was a negative effect of adjuvant chemotherapy for stage Ia. The risk reduction was 8% for stage Ib, 17% for stages II and III.

The effect of chemotherapy did not vary according to age, gender, PS, type of surgery and histology. When the drug combined with cisplatin was analyzed, the risk reduction was 20% for Vinorelbine, 7% for other biotherapies and 2% for tritherapies.

In the 1888 patients who received the combination of vinorelbine and cisplatin, the 5-year absolute benefit was 9% and the hazard ratio was 0.95 (0.76-1.20) for stage I vs 0.68 (0.56-0.83) and 0.62 (0.50-0.76) for stage II and III respectively. Finally, the Individual-data-based meta-analysis was updated in 2007 with a total of over 10,000 patients. It confirmed the significant effect of postoperative chemotherapy, with or without postoperative radiotherapy, with an overall benefit of 4% at 5 years.

In conclusion, the results of the recently reported large randomized studies of adjuvant chemotherapy suggest a 4 to 5% improvement of survival at 5 years. The LACE pooled analysis of the new generation of trials and, more recently, the update of the MRC-IGR meta-analysis confirmed the role of adjuvant chemotherapy in resected NSCLC except for stage Ia patients. The combination of vinorelbine in combination with cisplatin looks superior to older combinations. The results of the IALT-Bio program suggest to evaluate the expression of ERCC1 in order to determine which patients are more likely to benefit from chemotherapy. If these results are confirmed, we will enter the era of tailored therapy for resected NSCLC.

References

Adjuvant Chemotherapy for Young Women with Endocrine Non-responsive Early Breast Cancer: Any Issues?

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Introduction

Approximately 25% of newly diagnosed invasive breast cancer occurs in premenopausal women, with less than 10% of patients being less than 40 years of age at diagnosis [1].

The clinical behavior of breast cancer in younger women tends to be more aggressive than in older patients. Specifically, tumors in younger women present a higher grade and have a higher proliferating fraction and more vascular invasion than those occurring in older patients. Moreover, a higher proportion of patients are affected by tumors that do not express estrogen or progesterone receptors, while HER2 expression is apparently not influenced by age [2].

A review of the National Cancer Data Base reveals that patients younger than 35 years of age have more advanced disease at diagnosis and a poorer 5-year survival than older premenopausal patients. Similar findings have been reported from the National Cancer Institute SEER1 database, from the Finnish Cancer Registry, from the Southwest Oncology Group (SWOG) database, as well as from several studies described from single centers [3].

In early breast cancer, adjuvant treatment is decided according to risk and biological factors expressed on tumor cell surface. Guidelines from consensus conferences categorize patients in different groups and suggest treatment accordingly. For example, the 2007 St Gallen consensus meeting acknowledged 3 categories of tumors: highly endocrine responsive, incompletely endocrine responsive and endocrine non responsive tumors [4]. Each category is further divided into HER2 positive or HER2 negative, to assign Transtuzumab treatment.

Aim of this short review is to discuss treatments and related issues in young patients with early breast cancer, with a specific focus on endocrine non responsive tumors.

Adjuvant treatment of young, endocrine non-responsive HER2 positive patients

In patients with HER2 positive tumors, the use of adjuvant trastuzumab has become the standard of treatment since the publication of a pooled analysis of the 3 randomized clinical trials which demonstrated a 52% reduction in tumor recurrence, corresponding to a 17% increase in 4 years disease free survival (DFS). Moreover, a benefit in overall survival (OS) was also described, with a relative risk reduction of 33% (p=0.015). Importantly, the improvement in DFS and OS was observed for all subgroup of patients, including those of younger age [5]. Also the HERA trial confirmed the significant improvement, both for DFS and for OS, even if trastuzumab was given sequentially [6]. Again the advantage of trastuzumab administration was irrespective of patient’s age. Other schedules and combination are now under investigations, and the results of the extended trastuzumab schedule (2 years) are eagerly awaited. Moreover new molecular studies will help in selecting patients where the potentially more cardiotoxic anthracycline combination will give better results compared to non-anthracycline containing regimens.

Adjuvant treatment of young, endocrine non-responsive HER2 negative patients

Chemotherapy appears to be more effective for women younger than 50 years of age. Although this message is clearly given by the Early Breast Cancer Collaborative Trial (EBCCT) overview of most available randomized trials, it is not universally confirmed by individual large randomized studies [7]. Nonetheless, in young breast cancer patients with HER2 negative, endocrine non-responsive tumors, chemotherapy alone remains the treatment of choice. Recent molecular and immunohistochemical evidences identify patients affected by tumors which have a so called “basal type signature”, with a gene expression profile similar to those tumors occurring in BRCA1 mutated patients. These tumors do not express ER, PgR or HER 2 and are usually referred to as “triple negative” tumors. Triple negative tumors have a worse prognosis when compared to other histologies occurring in young women and new clinical trials with antiangiogenetic strategies are ongoing [8]. The use of platinum compounds or alkylating agents, which act through direct DNA damage, is warranted by some investigators, but data are controversial [9].

Time to treatment start

The proper time to commence adjuvant chemotherapy after primary surgery for breast cancer is unknown. The International Breast Cancer Study Group (IBCSG)
investigated the relationship between early initiation of adjuvant chemotherapy, ER status, and prognosis in 1,788 premenopausal, node-positive patients treated with classical CMF as adjuvant chemotherapy [10]. Among patients with ER-absent tumors, the 10-years DFS was 60% for the early initiation group (within 3 weeks from surgery) compared with 34% for the conventional initiation group (HR 0.49; 95% CI, 0.33 to 0.72; P= 0.0003). The results of this study show that premenopausal patients with ER-absent tumors and patients with tumors expressing some ER represent distinct populations with respect to responsiveness to early commencement of adjuvant chemotherapy. It should be pointed out, though, that subsequent retrospective analysis did not completely confirm these findings.

**Fertility issues in young patients receiving chemotherapy**

Fertility issues are of utmost importance in young patients with breast cancer. In a recently published retrospective analysis, 57% of women were seriously worried about chemotherapy induced infertility, and this influenced treatment decision in 29% of women [11].

Age at diagnosis, use of alkylating agents and cumulative chemotherapy dose are the most relevant factors which can predict the occurrence of chemotherapy related amenorrhea and infertility [12]. Even if amenorrhea could be useful for young women with endocrine responsive tumors, low estrogens levels are associated with severe impairment of quality of life. Premature ovarian failure is associated with somatic symptoms (hot flushes, vaginal dryness, premature osteoporosis) and psychological symptoms (reduction of libido and self esteem, sleep disorders) which alter body image and relationships.

New strategies of fertility preservation before chemotherapy are then warranted, including embryo freezing, egg freezing, oocyte in vitro maturation and ovarian freezing. Moreover trials with LHRH agonists or antagonists to protect the ovaries during chemotherapy are ongoing. Notably, most observational studies of pregnancy following breast cancer are reassuring and do not suggest that this carries a risk of higher breast cancer recurrence or death.

In conclusion, adjuvant chemotherapy with or without trastuzumab remains the main treatment modality for young women affected by endocrine non-responsive early breast cancer. Ongoing clinical trials will possibly ameliorate prognosis with more attention to quality of life issues in this special patient’s population.

**References**

Although the incidence of cancer in pregnancy is not fully known, it is estimated that 1:1000 pregnancies are complicated by a malignant neoplasm [1]. The most frequent tumors which complicate pregnancy are those that have a higher incidence during the childbearing age. Specifically, cancers of the breast, cervix, melanoma, lymphomas and acute leukemia are the most common gestational cancers [2]. Since there is a clear trend to postpone pregnancy to later in life, the co-association between cancer and pregnancy is becoming more frequent [3]

Accumulating evidence suggests that pregnancy per se is not a dismal prognostic variable. Survival appears to be similar between pregnant and non-pregnant cancer patients.

The treatment of malignant neoplasms during pregnancy should benefit the mother, especially in the case of curable malignancies, without damaging the fetus, whenever possible. Special care should be taken to retain mother’s reproductive system intact when possible, for future gestations. Surgery under general anesthesia is safe at all gestational ages, even if abdominal surgery can be associated with a higher incidence of fetal loss, particularly during the first trimester [4]. Care in maintaining adequate maternal pressure and blood volume should be taken, to avoid the risks of maternal and fetal hypotension.

Systemic chemotherapy can be safely administered during the second and third trimester [5]. Data in more than 100 patients with different neoplasms report that anthracyclines and alkylating agents are safe after the first trimester, with a high proportion of fetal wastage and should be avoided [9]. Few data are available about the administration of monoclonal antibodies during pregnancy. Prolonged trastuzumab treatment during pregnancy has been associated with oligo-anhydramnios and should be avoided, whenever possible [10]. Rituximab has a more favourable toxicity profile, but fetal lymphopenia has been described, so caution is mandatory [11, 12]. Hormonal treatment should be avoided during pregnancy. Data about Tamoxifen administration during pregnancy are scanty, but the occurrence of genital and systemic malformation after selective estrogen receptors modulators administration suggests caution [13]. Moreover the higher incidence of vaginal clear cell carcinoma in offsprings of mother treated with synthetic estrogens during the first trimester should be always kept in mind. Whenever an anti neoplastic systemic treatment is administered during pregnancy, the mother and her fetus should be strictly followed in a tertiary care obstetrical structure. Fetal well being and growth should be frequently monitored, due to the higher risk of intra uterine growth restriction and premature delivery associated with chemotherapy administration. A thorough follow up of the newborns, including cardiological, neuropsychological and reproductive assessment should be always planned, to acquire more information about the effects of in utero exposure to antineoplastic agents.

Radiotherapy should be avoided during gestation, particularly if it involves the subdiaphragmatic region [14]. Data about fetal risks of ionizing radiations during pregnancy are mainly derived from animal models or from the Japanese nuclear bombing cohort. Even if some controversy still remains, a threshold below 100 mGy (100 mSv) is usually considered safe for the onset of unwanted deterministic fetal damages, which include fetal death, fetal malformation or mental retardation. On the other hand the linear no-threshold hypothesis postulates that any exposure to ionizing radiations, even at low dosage could be harmful. These unwanted stochastic effects include the risk of fatal pediatric cancer before the age of 15 and can be estimated around 0.006%/mGy received during the intra uterine life. When treatment cannot be delayed, or the risk of fetal malformation of unwanted side effects is considered too high, termination of pregnancy is advisable although the prognosis does not appear to be different between patients who underwent pregnancy termination or elected to continue the pregnancy. Malignancies during pregnancy are a dramatic event with a profound impact on the life of the patient, the unborn child, the family and the treating caregivers. A multidisciplinary approach that includes an appropriate psychological support is essential for proper treatment of this difficult situation.
References

The incidence of ovarian cancer varies around the world. Ovarian cancer is the leading cause of death from gynecologic malignancy in the United States and Northwestern Europe. The age standardized incidence rate is highest in Northern Europe at 13.3 case per 100,000. In the United States, the American Cancer Society estimates 21,650 new cases and 15,520 deaths related to ovarian cancer in 2008. It is the fifth leading cancer site following breast, lung, colorectal, and endometrium. It also represents the 5th leading cause of cancer death in women following lung, breast, colorectal, and pancreatic carcinoma. Approximately one in seventy women will develop the disease and one in 100 will die secondary to its progression. The median age of diagnosis is 63. No accurate data is available as to the incidence and impact of the disease in the Arab world. According to WHO data, the age standardized incidence rate varies between 2.6 cases per 100,000 in Northern Africa and 5.3 per 100,000 in Western Asia. The mortality rate ranges between 1.8 and 3.4 per 100,000.

Surgical Staging for Clinical early-Stage Disease

The staging of epithelial ovarian cancer is based on histopathologic examination of tissues submitted at time of primary surgery. Women with early stage disease usually present with pelvic or adnexal masses. Initial evaluation would include a full history and physical exam, transvaginal ultrasound and/or CT scan or MRI and blood testing including serum Ca-125 level. This is usually followed by surgical exploration. The first step in the surgical procedure should include complete examination of the abdominal cavity followed by obtaining peritoneal washing. The pelvic mass with the affected ovary is then removed and sent to pathology for frozen section evaluation. Every attempt should be made to remove the mass intact without rupture and spillage of the contents into the peritoneal cavity in order to avoid upstaging. If a diagnosis of epithelial ovarian cancer is confirmed, a complete staging procedure will be performed including hysterectomy and contralateral oophorectomy, omentectomy, pelvic and paraaortic lymph node dissection and multiple peritoneal biopsies including sampling of the diaphragm. Performing a complete staging is important for prognostic as well as therapeutic reasons. First, approximately 30% of women with disease apparently confined to the ovary will have histologic evidence of metastatic disease and will require chemotherapy following surgery. Second, women with stage IA or IB and low-grade cancer do not need adjuvant chemotherapy. Other stage I patients might be candidates for an abbreviated adjuvant chemotherapy schedule. In these women, a complete and comprehensive staging might reduce the morbidity and cost of adjuvant therapy. Researchers from the European Organization for Research and Treatment of Cancer (EORTC) tested the efficacy of adjuvant chemotherapy for early-stage ovarian cancer in phase III randomized trial. They found that in optimally staged patients, chemotherapy did not improve survival. On the other hand, chemotherapy was associated with improved recurrence-free survival in the non-optimally staged group.

Unfortunately, despite these recommendations, a large number of women with early stage ovarian cancer do not undergo complete staging. Studies have shown that the specialty of surgeon performing the staging has a significant impact on how adequately the staging is performed. Complete staging is performed in 97% of patients cared for by a gynecologic oncologist, compared to 35-52% of patients evaluated by other surgeons. In a subset of young women with early ovarian cancer, fertility preserving surgery is an acceptable therapy. Removal of the pelvic mass with the involved ipsilateral adnexa, while preserving the uterus and contralateral ovary, are recommended in a woman who desires future fertility and who has a low-grade lesion confined to one ovary. Complete surgical staging should still be performed to rule out peritoneal or lymphatic spread of the cancer.

Surgical Management of Advanced Stage Disease

Primary Tumor Debulking Surgery

Women with advanced stage ovarian cancer frequently present with large volume ascites and extensive pelvic and intra-abdominal disease. In 1934, Meig was the first to describe primary debulking or cytoreduction in ovarian cancer. Pemberton in 1940 and Munnell described similar concepts in 1957. Griffiths was the first to publish data correlating the size of residual disease and survival in women with advanced ovarian cancer. The beneficial effect of tumor debulking has been explained based on a number of theoretical hypotheses. First, it is believed that reducing the volume of the tumor will optimize the blood flow to the residual masses thus improving drug delivery, increasing the growth fraction of the tumor and improving response of the cells to chemotherapy. Second, since the number of chemoresistant cells is proportional to the total number of neoplastic cells, reducing the total number of cells will decrease the number of chemoresistant clones.
the fractional cell kill hypothesis implies that the efficiency of chemotherapeutic agent is dependent on drug dosage and number of viable neoplastic cells. Removing a large percentage of the viable neoplastic cells surgically will leave a smaller number of cells for the chemotherapy to kill. Finally, it has been speculated that tumors can suppress the patient immune system and removing them may enhance immune function.

Since the initial publication by Griffiths in 1972, there have been a large number of retrospective studies that have confirmed a negative correlation between size of residual disease and survival. In a recently published meta-analysis of 81 cohort studies that included 6885 patients with stage III or IV ovarian cancer treated with surgery and platinum based therapy, Bristow et al showed a correlation between the proportion of maximal cytoreduction and median survival. They reported a 5.5% increase in median survival for each 10% in increase in maximal cytoreduction. The median survival was 22.7 months in patient populations with <25% maximal cytoreduction compared to 33.9 months in those with >75% maximal cytoreduction. Extended survival exceeding 4 years has been reported in stage IIIC ovarian cancer patients who were optimally debulked prior to receiving chemotherapy.

There is an ongoing argument whether the beneficial effect of surgical cytoreduction are related to the surgical effort or is inherent to the tumor biology. Some have proposed that the biologically less aggressive tumors are more amenable to optimal debulking but are also more likely to have a better prognosis independent of the surgical effort. A number of authors have tried to refute that argument by showing that the use of radical surgical procedures to achieve optimal debulking in more aggressive tumors is not associated with a worse prognosis. They have also shown that the size of residual disease but not the extent of disease at initiation of surgery is an independent prognostic factor. Finally, a number of papers have also proved that the institution and surgeon’s experience are important in achieving optimal surgical results and improving the survival of women with advanced ovarian cancer.

The goal of surgical debulking is to remove all gross disease since this is associated with the best survival outcome. When left with macroscopic residual disease after tumor debulking, patients with largest residual tumor <1 cm tend to survive longer than those with >1 cm residual disease. Cytoreduction for advanced disease often requires removal of large pelvic tumors with en bloc resection of uterus, ovaries and rectosigmoid. Omentectomy, bowel resection and removal of extensive peritoneal and diaphragmatic implants. The use of the Cavitron Ultrasonic Surgical Aspirator (CUSA) and Argon Beam Coagulator can sometimes increase the success of cytoreduction. Significant surgical expertise and special training are required to perform radical ovarian cancer cytoreductive procedures. In addition, these women are usually older and have other medical illnesses. Optimal and aggressive perioperative care, with adequate intensive care support, is essential for a successful outcome.

Secondary Tumor Debulking Surgery

In women whose primary surgery was suboptimal, the role of secondary surgery after primary surgery and 3 cycles of chemotherapy was investigated in 2 independent randomized trials one in Europe by the EORTC and the second in the United States by investigators from the Gynecologic Oncology Group (GOG)15,16. The findings of the 2 studies were conflicting. The EORTC study did find that women who underwent optimal secondary surgery had an improved survival. These findings were not confirmed by the GOG study. One possible explanation is the difference in maximal surgical effort at time of primary surgery. For women whose primary surgery involved a minimal attempt at tumor debulking, a secondary debulking surgery may be valuable in improving patients’ overall outcome. On the other hand, the role of secondary debulking may be limited in women whose primary surgery involved a maximal surgical effort even though optimal debulking could not be achieved.

Interval Tumor Debulking Surgery

The use of neoadjuvant chemotherapy prior to any surgery has been reported in women with ovarian cancer cases who are too sick to undergo primary surgery. In addition, some authors have proposed using this approach in cases where extensive metastatic disease interferes with optimal primary cytoreduction. Proponents of this approach argue that the use of chemotherapy will increase the chances of achieving an optimal cytoreduction at time of interval surgery. In addition, the surgical complications of the interval debulking surgery are reduced because the tumor load is smaller and the patients are in a better physical condition. However, not everyone is supportive of this approach. In a review of the published studies, Bristow and Chi concluded that neoadjuvant chemotherapy with interval debulking is associated with inferior survival compared to primary surgery. However, they did find that in patients who underwent interval debulking, increasing percent maximal cytoreduction is positively associated with median survival.

Surgical Management of Recurrent Disease

Despite the excellent response rates (around 70%) to primary therapy, over two thirds of women with advanced ovarian cancer suffer from disease recurrence. Treatment of recurrence is influenced by a number of factors including initial tumor histology, outcome of primary surgery, response to primary chemotherapy, time to recurrence, site of recurrence and coexisting medical illnesses. Women who recur over six months after initial response to platinum based chemotherapy, are considered to be platinum sensitive. In this subgroup, one option of salvage treatment includes reinduction with a platinum compound. Other drugs proven to be effective in the salvage therapy of recurrent ovarian cancer are topotecan, pegylated liposomal doxorubicin (doxil), gemcitabine, docetaxel, paclitaxel, navelbine, oral etoposide, hexamethylmelamine, ifosfamide, tamoxifen and bevacizumab. Women who fail within six months of platinum-based chemotherapy are considered platinum resistant. They can be offered one of the above listed drugs. Unfortunately, their disease tends to respond poorly to most drugs and their life span is usually limited.

A selected group of patients with recurrent disease may benefit from secondary cytoreduction. This includes women who have: a longer disease-free interval, a good response to initial treatment, a limited number of recurrent tumors that are surgically accessible, and a good physical condition. The patient should also be willing to be treated with chemotherapy (or less commonly radiation therapy) after recovery from surgery. The goal of secondary surgery for recurrent disease is resection of all gross disease. Prolonged survivals have been reported in some of these patients. A number of factors have been associated with a higher likelihood of optimal secondary cytoreduction as well as prolonged survival. These include: younger age, longer recurrence free interval, complete clinical response to primary platinum chemotherapy and a good performance status. Two ongoing randomized clinical trials one by GOG and one by EORTC are evaluation the role of surgery for recurrent disease.

In conclusion, surgery plays an important role in the management of epithelial ovarian cancer. At diagnosis, optimal staging or debulking surgeries are important to secure patients the best survival outcome. At recurrence, surgery needs to be considered as an option in some patients. Many studies have shown that the
expertise of the specialist surgeon has a significant impact on survival. The initial staging and resection in primary disease as well as the appropriate decision and surgical procedure in recurrent disease are best handled by specialized surgeons who have been trained in the field and who routinely manage ovarian cancer in their practice.

References

2. Young RC et al. JAMA1983:250
5. Goff BA et al. Gynecol Oncol 2006;103
6. Griffiths CT. Natl Cancr Inst Monogr 1975;42
8. Ozols RF et al. J Clinic Oncol 2003;21
17. Hou JY et al. Gynecol Oncol 2007;105
18. Vergote I et al. Oncology, 2005;19
19. Bristow RE, Chi DS. Gynecol Oncol 2006;103
20. Munkarah AR, Coleman R. Gynecol Oncol 2004;95
Targeted Therapy in Ovarian Cancer

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The disease related mortality associated with epithelial ovarian cancer is high. The majority of patients have advanced stage disease at diagnosis. Despite good response to primary therapy, a large proportion of patients will suffer from a recurrence. A number of chemotherapy agents have shown efficacy at relapse. Treatment of recurrent disease with platinum-based therapy continues to be very effective in patients with platinum sensitive disease. Other chemotherapy options include taxanes, topotecan, pegylated liposomal doxorubicin, gemcitabine, navelbine, oral etoposide, capcitabine and hexamethylmelamine. Newer promising agents include trabectedin, patupilone and pemetrexed. Therapy targeting specific molecular changes in the neoplastic cells has opened in new era in cancer treatment. In this abstract we summarize some of these applications in ovarian cancer.

Molecular changes in epithelial ovarian cancer

Advances in molecular biotechnology have shed more light on the genetic changes associated with ovarian carcinogenesis and have helped to identify molecular changes that impact tumor growth and progression. These molecular changes have proven to be prognostic indicators and some are potential therapeutic targets. Protein kinases are enzymes that catalyze the phosphorylation of tyrosine, serine and/or threonine residues of specific proteins inside cells. Deregulation of protein kinase signaling has been associated with malignant transformation and progression in many organs including the ovary.

Tyrosine Kinases
Receptor Tyrosine Kinases
Protein tyrosine kinases include transmembrane receptor kinases and nonreceptor tyrosine kinases. The receptor tyrosine kinases (RTKs) are glycoproteins that possess an extracellular ligand–binding domain, a single hydrophobic transmembrane domain and an intracellular catalytic domain containing regulatory sequence. There are many families of RTKs including receptors for epidermal growth factor (EGF), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor and hepatocyte growth factor. EGFR overexpression has been reported in 35% to 70% of patients with epithelial ovarian cancer 1-3. The prognostic significance of EGFR overexpression in EOC is not clear. Similarly, HER2 overexpression in ovarian cancer varies widely with overexpression rates reported in 20% to 30% of cases 4. The VEGF family of proteins is a main regulator of angiogenic process that is essential for tumor growth and metastasis. Angiogenesis is also a key component of the normal physiologic function of the ovaries during reproductive life. In fact, the maturation, growth and regression of the ovarian follicles and corpus luteum are highly dependent on angiogenesis. Coordinated changes in levels of VEGF occur during the menstrual cycle 5. There are six known VEGF proteins: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, placenta-derived growth factors 1 and 2 (PIGF). There are 3 known VEGF tyrosine kinase receptors: VEGFR-1 (FLT-1), VEGFR-2 (KDR/FLK-1), and VEGF-3 (FLT-4). VEGF-A is the most well characterized member of the family; it binds to VEGFR-1 and -2 and can form heterodimers with VEGF-B 6. Overexpression of VEGF has been demonstrated in many malignancies including EOC 7,8.

Nonreceptor Tyrosine Kinases
Nonreceptor tyrosine kinases are cytoplasmic proteins that transduce extracellular signals to downstream pathways that regulate cell growth and participate in multiple carcinogenic pathways promoting proliferation, adhesion, cell survival and angiogenesis. Unlike RTKs, they lack transmembrane domains and receptors to bind ligands. One of the first oncoproteins described, src, belongs to this family. Overexpression of src has been demonstrated in 93% of advanced-sage ovarian cancer and in more than 80% of ovarian cancer cell lines 9.

Serine-Threonine Kinases
These kinases are almost all intracellular and include raf, Akt/protein kinase B and mitogen activated protein extracellular regulated kinase (MEK). mTOR (mammalian target of rapamycin; also known as FRAP, RAFT1 and RAPT1) is a serine/threonine kinase involved in the regulation of a number of growth related cellular functions. mTOR activity seems to be regulated by PI3K/Akt. The PI3K/Akt pathway is upregulated in approximately 30% of ovarian cancer 10.

Targeted therapy in epithelial ovarian cancer

Many strategies are being developed to target the molecular changes described above. The goals are to knockdown or inhibit the function of the overexpressed proteins that are believed to promote tumor growth and progression. The two main strategies used are small molecules inhibitors and monoclonal antibodies to bind the ligand and/or receptor. Other approaches have included ligand-conjugated toxins, antisense oligonucleotides and vaccines.
Targeting EGF and Receptors

Small molecules such as gefitinib, erlotinib and lapatinib have been used in clinical trials with limited efficacy as single agent therapy. Monoclonal antibodies cetuximab, trastuzumab, pertuzumab have also been investigated in combination with chemotherapy both in the primary treatment setting as well as in patients with recurrent disease. The data is not sufficient to make any definite conclusions however most studies has shown no significant added efficacy with these drugs 11-16.

Targeting VEGF

Bevacizumab, the humanized monoclonal antibody that binds VEGF-A, is the first targeted agent to show significant activity in epithelial ovarian cancer. A number of phase II trials investigated bevacizumab as single agent or in combination with low dose chemotherapy and showed significant efficacy in recurrent ovarian cancer 17-19. An increased incidence of bowel perforation has been reported as a treatment associated toxicity. Currently bevacizumab is being investigated in the setting of primary therapy in combination with chemotherapy. There are two large phase III randomized trials being conducted in the US and in Europe looking at the combination of bevacizumab with paclitaxel and carboplatin in the primary treatment of advanced stage EOC. Aflibercept, also known as VEGF trap, is a fusion protein of the extracellular ligand-binding domains of VEGFR-1 and VEGFR-2 fused to the Fc portion of immunoglobulin IgG1. It binds VEGF-A, VEGF-B and PIGF-1 and -2. It has shown promising activity as a third or fourth line therapy in patients with recurrent advanced EOC 20. Sorafenib, initially developed as Raf inhibitor, has also been found to inhibit VEGFR-2 and -3, FLT-3, c-kit and PDGFR-b. Early data have shown promising activity in recurrent ovarian cancer when used in combination with gemcitabine21. A number of other inhibitors are being investigated as monotherapy or in combination with chemotherapy in EOC. These include cediranib, sunitinib and pazopanib.

Targeting src

In ovarian cancer cell lines, src inhibition has been shown to enhance taxane-mediated toxicity. It has also exhibited a potent antiangiogenic activity. Currently, the src inhibitor, dasatinib, is being investigated in combination with carboplatin and paclitaxel in a phase I trial including patients with advanced stage ovarian cancer 22.

Targeting mTOR

The mTOR inhibitors, everolimus and temsirolimus, are being investigated as single agent as well as in combination with chemotherapy in patients with recurrent EOC.

References

Management of Localized Pancreas Adenocarcinoma

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Summary

The term localized disease as it applies to pancreas adenocarcinoma encompasses distinct entities with varied prognosis and therapeutic recommendations. These include three disease categories (1) disease that is localized and resectable, (2) localized disease that is borderline resectable, and (3) unequivocally unresectable pancreas cancer, all representing a continuum. The incorporation of systemic chemotherapy into the management of pancreas cancer at all stages has become standard of care, and the basis for this is discussed with reference to the major clinical trial landmarks. The role of radiation therapy (in association with concomitant chemotherapy) in the management of localized pancreas cancer has however become less clear and represents an area of management confusion in this disease. Going forward, with the future hope and expectation of new and improved systemic agents, loco-regional tumor control and hence, chemoradiotherapy, is anticipated to have a greater role and impact.

Introduction

Pancreas adenocarcinomas is a very challenging malignancy. About 38,000 people were anticipated to be diagnosed in 2008 in the United States and over 200,000 worldwide[1]. In the US the expected mortality this past year was approximately 33,000. Many factors contribute to these statistics – insidious clinical presentation and late symptom manifestation, lack of screening and early detection and limited effectiveness of the best currently available therapies. Surgical removal of locally-confined disease is the only realistic curative option. Even in that circumstance however, the relapse rate is high such that surgical resection followed by adjuvant chemotherapy is viewed by many as delaying rather than eliminating disease recurrence. Similarly, for patients with localized disease which is unresectable and unequivocally T4, treatment is essentially palliative in intent.

In discussing the management of localized pancreas cancer – with regard to both standard therapies and areas of controversy – it is important to delineate various categories which are distinct both with regard to prognosis and therapeutic approach. The most important distinction to be made is between resectable and unresectable localized disease. For localized disease that is resectable, the focus will be one key question: (1) What is the benefit of adjuvant therapy. For localized disease that is unresectable, there is a distinction to be made between borderline unresectable disease and disease that is unequivocally inoperable. For discussion of these categories, the focus will be on two questions: (1) What is the role of (chemo)radiation therapy?, (2) What is the optimal systemic therapy or combination of systemic drugs?

Localized Resectable Pancreas Adenocarcinoma

In the case of pancreas cancer, the precedent for adjuvant chemotherapy has been established relatively recently although the historical precedent for adjuvant chemoradiotherapy and chemotherapy dates back to the Gastrointestinal Tumor Study Group (GITSG) trial[2]. Older small randomized studies of adjuvant systemic therapy (without chemoradiation) using a variety of 5-FU-based regimens did not show a significant survival benefit compared to observation[3-5]. In 2004, Neoptolemos et al. published the updated report of the ESPAC-1 trial in the New England Journal of Medicine evaluating the role of adjuvant therapy in pancreas cancer[6]. The complex study design allowed the investigators to isolate and compare the relative benefits of chemotherapy and chemoradiation. The median survival was 20.1 months (95% CI, 16.5 to 22.7 months) for those who received chemotherapy and 15.5 months (95% CI, 13.0 to 17.7 months) for those who did not receive chemotherapy (hazard ratio for death, 0.71). Two-year and five-year survival estimates were 40 percent and 21 percent, respectively, among patients who received chemotherapy compared to 30 percent and 8 percent, respectively, among patients who received no chemotherapy. The investigators concluded that 5-FU-based chemotherapy offered a survival advantage and that chemoradiation offered no such benefit and may in fact be detrimental to outcome.

Given that gemcitabine has modestly more efficacy in metastatic disease than 5-FU, the rationale was strong to consider it’s use in the adjuvant setting. The RTOG 9704 trial compared gemcitabine and 5-flourouracil in a 451 patient U.S Study[7]. The chemotheraphy was given for one month prior to, and 3 months following chemoradiation. There was a benefit to gemcitabine but only for patients with tumors in the head of the pancreas. For patients with pancreatic head tumors the median survival was 20.5 months and a 3-year survival of 31% in the gemcitabine group vs 16.9 months and 22% in the fluorouracil group (HR, 0.82 [95% CI, 0.65-1.03]; P = .09). This reached statistical significance when a multivariate analysis was performed evaluating pre-planned stratified variables. These included nodal status, which was found to strongly affect survival (P = .001)
and the effect of gemcitabine which yielded a HR of 0.80 (95% CI, 0.63-1.00; P = .05) toward improved survival.

Perhaps the best data with regard to adjuvant gemcitabine is derived from the CONKO-001 study, published in 2007 and recently updated[8, 9]. The design of the CONKO-001 trial was somewhat purer than the RTOG study as none of the patients received chemoradiation. It was a direct comparison of chemotherapy versus observation following resection. The trial met it’s primary endpoint with disease free survival being 13.4 months in the gemcitabine arm and 6.9 months in the observation arm, p < 0.001. Estimated disease-free survival at 3 and 5 years was 23.5% and 16.0% in the gemcitabine group vs. 8.5% and 6.5% in the observation group, respectively. Gemcitabine significantly improved median overall survival (22.8 months versus 20.2 months, P=0.005). Estimated survival at 3 and 5 years was 36.5% and 21.0% for the gemcitabine-treated group compared to 19.5% and 9% for the observation group.

To summarize, we now have level 1 evidence supporting gemcitabine’s use in the adjuvant setting for resected pancreas adenocarcinoma. Ongoing and planned adjuvant phase III adjuvant studies in Europe will address the benefit of the addition of erlotinib to gemcitabine (CONKO-006 and RTOG 0848) and capecitabine to gemcitabine (ESPAC-4). The role of chemoradiation in the adjuvant treatment of pancreas cancer has diminished both in the context of stronger evidence for systemic therapy alone and also a fuller understanding of the biologic behavior of this disease. The expectation however is that when systemic therapy improves in this disease, loco-regional tumor control will gain in relative importance.

**Locally Advanced Unresectable Pancreatic Adenocarcinoma (LAPC)**

For a pancreatic tumor to be clearly resectable, the following three criteria need to be satisfied[10]: no evidence of distant metastases, a clear fat plane around the celiac and superior mesenteric arteries (SMV) and patent of the superior mesenteric and portal veins (SMV-PV). Patients with unresectable disease have encasement of celiac or SMA, defined as involvement of > 180°, or occlusion of the SMV-PV confluence. In recent years a subset of patients have been defined as having disease that is borderline resectable, for whom surgical resection may yet be a possibility in their management. Given that there is little to be gained from attempting surgery when the chances of obtaining negative margins are not high, there is a strong rationale for a neoadjuvant approach to this setting.

The MD Anderson group recently reported their experience of neoadjuvant therapy in eighty-four patients who were borderline-resectable based on their own anatomic criteria (in addition to another seventy-six patients who they deemed borderline resectable on the basis of performance status and suspicion of metastatic disease)[11]. Thirty-two (38%) of the patients who were borderline resectable on anatomic criteria were able to undergo a (partial) pancreatectomy following neoadjuvant therapy, the vast majority of whom (97%) had clear margins. Similar to other reports relating to this specific entity[12, 13], this was not a prospective study, and in the absence of a control group it is impossible to know whether these patients did better or worse following the addition of neoadjuvant therapy. In addition, there was a heterogeneity in the neoadjuvant therapy used, although all these patients did receive chemoradiation. Clearly prospective randomized studies would of course be ideal but it is unlikely that the benefit of neoadjuvant therapy could be purely quantified, as there would be ethical concerns about having a ‘straight-to-surgery’ control group in a situation where the chances of obtaining negative margins are not high.

For disease that is clearly unresectable according to the criteria mentioned above, the role of surgery with curative intent is minimal except for the anecdotal patient. Likewise the role of radiation has grown increasingly controversial in this setting, as in the adjuvant setting, largely due to a fuller appreciation of the biology of pancreas cancer and the demonstration of benefit of systemic therapy, albeit in relative terms, modest. These issues diminish the importance of local control measures for this cohort of patients in general, based on the assumption that the majority of them will have sub-radiologic metastatic disease, which will in time be the main determinant of their prognosis.

The foothold of chemoradiation for LAPC was established on the basis of a number of small clinical trials stretching back to the 1960’s. Two of these studies demonstrated a survival benefit for (5-FU based) chemoradiation compared to radiotherapy alone[14, 15]. Two other studies from the same era compared chemotherapy alone to chemoradiation. In a trial by the Gastrointestinal Tumor Study Group (GITSG) a benefit was demonstrated for chemoradiation plus chemotherapy compared to chemotherapy alone[16]. The chemotheraphy consisted of streptozocin, mitomycin and 5-FU and the 1-year survival benefit was 41% compared to 19%. The other trial, by the Eastern Cooperative Oncology Group (ECOG)[17], compared 5FU-chemoradiation with chemotherapy alone, failing to demonstrate a survival benefit.

The value of chemoradiation in LAPC has not been quantified in the modern clinical trial epoch. In an attempt to address this question in the era of gemcitabine a phase III study was performed by the FFCD – SFRO (Fédération Francophone de Cancérologie Digestive - Société Française de Radiothérapie Oncologique) in France[18]. In this study, the first for nearly 20 years to address this question, 119 patients (of a planned 176) were randomized to undergo induction chemoradiation (with 5-FU 300 mg/m2/24 h as a continuous infusion, day 1–5 every week and cisplatin, 20 mg/m2/d, day 1–5 at week 1 and 5) followed by gemcitabine, or straight to chemotherapy with gemcitabine. The study was stopped prior to its planned enrollment due to an inferior survival in the chemoradiation group (median survival 8.6 v 13 months, p = 0.014). Although this study is not a definitive answer to the question of chemoradiation, it does add to the growing body of opinion that the benefit of chemoradiation in LAPC is most likely confined to a carefully selected subgroup. Recently a not dissimilar study design by ECOG[19] of initial systemic therapy compared to chemoradiation was reported comparing gemcitabine alone (1,000 mg/m2 weekly x 3 every 4 weeks for 7 cycles) to chemoradiation (RT 50.4 GY in 28 fractions plus gemcitabine 600 mg/m2 weekly x 6) followed by 5 cycles of gemcitabine alone (1,000 mg/m2 weekly x 3 every 4 wks). The trial was stopped early due to slow accrual (N = 74, out of a planned 316). The median survivals were 9.2 months (95% CI 7.8 - 11.4) and 11.0 months (95% CI 8.4 - 15.5) for the two arms respectively (p=0.044).

In an interesting attempt to tease out the benefit of chemoradiation, investigators from the Groupe Coordinateur Multidisciplinaire en Oncologie (GERCOR)[20] performed a retrospective analysis of 181 patients with locally advanced PAC who had been entered on prior prospective GERCOR studies and who had been offered chemoradiation (at the discretion of the investigator), but only if they had remained metastasis-free after a 3-month period. For those patients who were metastasis-free after initial chemotherapy, there was a survival advantage if they proceeded to chemoradiation compared to those who continued with chemotherapy alone (median OS 15.0 and 11.7 months, respectively; P = .0009). These data suggest that radiation may offer a survival benefit in selected patients who have disease that is proven to be localized after a test of time. This is an attractive concept as it allows patients to be selected for chemoradiation whilst receiving...
systemic therapy for their disease and also gives time for the logistics of the chemoradiation to be organized.

To summarize, the role of chemoradiation in the management of locally advanced, clearly unresectable pancreas cancer, has changed in recent times with a trend towards induction systemic therapy. This seems to be the most pragmatic approach for selecting out the patients who will genuinely benefit from local therapy and avoiding intensive chemoradiation in patients who in all likelihood will not benefit from it.

Leaving aside the chemoradiation question, what is the best systemic therapy for LAPC? Gemcitabine became established as a cornerstone drug in pancreas adenocarcinomain 1997 following a phase III study which demonstrated an improvement in clinical benefit and survival (a secondary endpoint in the study) compared to 5-FU[21]. Progress since then has been modest and mixed. Phase III co-operative groups studies exploring the addition of the biologic agents, bevacizumab[22] and cetuximab[23], to gemcitabine in advanced pancreas adenocarcinoma have been negative in this disease, a particularly disappointing outcome given their demonstrated efficacy in other gastrointestinal cancers and the preclinical rationale for their use in PAC.

Cytotoxic combinations of gemcitabine with capecitabine and platinum agents do appear to offer a small incremental benefit, particularly in patients with good performance status. Heinemann et al. performed a randomized study of gemcitabine in combination with cisplatin versus gemcitabine alone[24]. This study showed an overall survival benefit which was not statistically significant (7.5 v 6.0 months, HR = 0.80; P = 0.15). A meta-analysis of trials indicated a significant survival benefit for combination regimens when gemcitabine was either combined with platinum analogs (HR 0.85; 95% CI: 0.76 - 0.96, p = 0.010) or fluoropyrimidines (HR 0.90; 95% CI: 0.81 - 0.99, p = 0.030). In a subgroup analysis patients with a good PS appeared to benefit from cytotoxic combinations (HR = 0.76; 95% CI: 0.67 - 0.87; p < 0.0001), whereas patients with a poor PS seem to have no survival benefit from combination chemotherapy[25]. The first trial to show a survival benefit for any combination therapy in pancreas cancer and which led to FDA approval of this combination in the front-line treatment of pancreatic cancer in 2005, was a study by Moore et al., in which 569 patients with untreated locally advanced or metastatic pancreas cancer were randomized to receive gemcitabine with either erlotinib or placebo[26]. There was a very modest but statistically significant improvement in progression-free (HR .77,95% CI, 0.64–0.92,P=0.004), one-year survival (23% v 17%; P=.023) and median overall survival (6.24 months v 5.91 months, HR 0.82, 95% CI, 0.69–0.99,P=0.038) favoring the erlotinib arm.

References


Mantle cell lymphoma (MCL) is considered incurable; with a reported median survival of 3 years after conventional chemotherapy.1 Therapeutic options in MCL were very limited until the mid 1990s when autologous stem cell transplantation (ASCT) became available for this especially poor-risk subtype of lymphoma. The Omaha group was the first to show the potential efficacy of this intensive modality in MCL.2 Since then, numerous studies have been published documenting the feasibility and potent anti-lymphoma activity of ASCT in this entity, in particular if used as part of first-line treatment. However, almost all trials were uncontrolled and suffered from small patient numbers and limited observation times.3

Only recently Dreyling and co-workers were able to demonstrate the superiority of ASCT over standard CHOP chemotherapy with interferon maintenance in terms of progression-free survival (PFS) in a prospective randomized phase-III study. Nevertheless, with a median follow-up of 34 months, a plateau in the survival curve was not seen even in this trial, and a significant survival benefit could not be shown. In this trial patients 65 years of age or younger with advanced-stage MCL were assigned to ASCT or IFNα after achievement of complete or partial remission by a CHOP-like induction therapy. Sixty-two of 122 patients proceeded to ASCT and 60 received IFNα. Patients in the ASCT arm experienced a significantly longer PFS with a median of 39 months compared with 17 months for patients in the IFN arm (P = 0.0108). The 3-year overall survival (OS) was 83% after ASCT versus 77% in the IFNα group (P = 0.18). 4

Given the superiority of both ASCT and rituximab-supplemented therapy over conventional treatment in MCL, both modalities have been combined in a prospective phase II study. Thirty-four patients with newly diagnosed MCL were treated with a sequential dose-escalating therapy comprising standard chemotherapy for remission induction, intensive ara-C-containing chemotherapy for mobilization of stem cells, and myeloablative therapy followed by ASCT. The myeloablative regimen consisted of total body irradiation and high-dose cyclophosphamide supplemented with two doses (375 mg/m2) of rituximab. Outcome parameters (toxicity, clinical and molecular response as assessed by allele-specific IGH real-time quantitative polymerase chain reaction (RQ-PCR), EFS, and OS) were compared with those of 34 historical controls treated identically but without rituximab. Whereas engraftment, toxicity and clinical response were not different from those in controls, EFS was significantly increased with rituximab (4-year EFS 83% versus 47%, P = 0.036). The difference in OS was not statistically significant (4-year OS 87% versus 77%). This was associated with a trend for a superior molecular response rate in 11 study versus 10 control patients with a marker available (73% vs. 30%, p=0.086) despite similar levels of lymphoma contamination of the stem cell inocula infused. It was concluded that incorporation of two standard doses of rituximab into the myeloablative regimen might improve outcome of upfront ASCT for MCL, allowing long-term disease control to an extent previously not reached in this disease.5

Based on series reporting a high efficacy in MCL of regimens containing cytarabine, both in terms of prolonged EFS and, in combination with rituximab, in terms of a high rate of clinical and molecular remission and tumor-cell free stem cell products, the second Nordic MCL protocol (NLG MCL-2) was launched in 2000, with the aim of increasing the rates EFS, PFS, and OS, and of molecular remission and PCR-negative stem cell products. In the 2nd Nordic MCL trial, 160 consecutive, untreated patients younger than 66 years were treated in a phase II protocol with dose-intensified induction immunotherapy with rituximab (R) + cyclophosphamide, vincristine, doxorubicin, prednisone (maxi-CHOP), alternating with R + high-dose cytarabine. Responders received high-dose chemotheraphy with BEAM or BEAC (carmustine, etoposide, cytarabine, and melphalan/cyclophosphamide) with R-in vivo purged autologous stem cell support. Overall and complete response was achieved in 96% and 54%, respectively. The 6-year OS, EFS, and PFS were 70%, 56%, and 66%, respectively, with no relapses occurring after 5 years. Multivariate analysis showed Ki-67 to be the sole independent predictor of EFS. The non-relapse mortality was 5%. The majority of stem cell products and patients assessed with PCR after transplantation were negative. Compared with the historical control, the Nordic MCL-1 trial, the EFS, OS, PFS, the duration of molecular remission, and the proportion of PCR-negative stem cell products were significantly increased (P < .001). The emerging PFS plateau after 5 years could raise the hope that a proportion of younger MCL may be cured, but this will take longer follow-up to demonstrate than the median follow-up of only 3.4 years. 6

Few data are available on the results of myeloablative conditioning and allogeneic HCT for mantle cell lymphoma. The largest series from MDACC, EBMT, and Baltimore reported on 16, 22, and 19 patients with MCL, respectively. OS was > 50% at 2 or 3 years and indicated a potential role for allogeneic HCT in this disease. 7-9

Haematopoietic Stem Cell Transplantation in Mantle Cell Lymphoma

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The results of nonmyeloablative allogeneic HCT for relapsed or refractory MCL are promising. In one study, subjects with advanced recurrent mantle cell lymphoma, 89% of whom had chemosensitive disease, were treated with non-myeloablative allogeneic HCT. Complete remission was obtained in 17 of the 18 patients with a day-100 mortality of zero. At a median follow-up of 26 months, estimated three-year event-free survival was 82%. The high response and low relapse rates with this approach suggest that MCL is susceptible to graft-versus-tumor response.

Aggressive MCL has a poor prognosis; however, long-term disease-free survival is possible after rituximab-containing autologous transplantation for patients in first remission, and after non-myeloablative allogeneic stem cell transplantation for patients with relapsed or refractory disease.

References


The Role of Biologicals in the Management of Metastatic in Colorectal Cancer

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The management of patients with metastatic colorectal cancer (CRC) has changed dramatically over the last years, with increasing chances of prolonged survival. The median survival of patients with unresectable metastatic disease approaches now 24 months. The development of new cytotoxic and targeted agents; as well as the multidisciplinary management of patients with resectable and initially non-resectable metastases contribute to the progress. The development of the cytotoxic agents irinotecan, oxaliplatin and capcitabine and of the biological agents bevacizumab, cetuximab and panitumumab has clearly increased the therapeutic options for patients with metastatic colorectal cancer. Several other new agents are far advanced in development in colorectal cancer. Resection of liver- or lung metastases can lead to cure of patients with metastatic colorectal cancer. Complete resection of metastases leads to long term survival rates of 30-40%. Due to more active new combination regimens, some patients with initially unresectable liver metastases can also be downsized to resectable disease, leading to chances for cure in these patients.

The new targeted agents have been introduced recently in the therapeutic regimens of patients with metastatic colorectal cancer. There is a strong preclinical and clinical rationale for the use of Vascular Endothelial Growth Factor (VEGF) inhibitors in colorectal cancer. The anti-VEGF monoclonal antibody, bevacizumab, increases the activity of a variety of active cytotoxic regimens in metastatic CRC. It has been shown in randomized phase 3 trials that bevacizumab, when combined with irinotecan plus 5-fluorouracil (5-FU)/ leucovorin (LV) in the first-line treatment of metastatic CRC and with FOLFOX (5-FU/LV/oxaliplatin) in second-line treatment leads to an increased median survival, progression-free survival (PFS) and response rate (RR) compared to the cytotoxic chemotherapy alone. Moreover, it has been demonstrated in a few randomized phase 2 studies and in a combined analysis of these phase 2 studies that bevacizumab increases the activity of 5-FU/LV in the first-line treatment of metastatic CRC.

A large randomized phase 3 study of FOLFOX or capcitabine/oxaliplatin ± bevacizumab in the first-line treatment shows that capcitabine is as effective as IV 5-FU/LV when combined with oxaliplatin and that bevacizumab increases the PFS of the fluoropyrimidine/oxaliplatin combination. Based on these data it is today accepted that bevacizumab increases the activity of the different cytotoxic agents when these agents are combined. Bevacizumab is safe in colorectal cancer. It does not increase the typical chemotherapy related side effects, but is has some specific side effects: arterial hypertension, proteinuria, mucosal bleeding (most frequently epistaxis), arterial thromboembolic events, seldom gastrointestinal perforation and also wound healing problems.

Aflibercept (VEGF trap) is engineered soluble receptor made from extracellular domains of VEGFR1 and VEGFR2, binds to all isoforms of VEGF and to placental growth factor. Aflibercept is under active investigation in phase 3 in combination with standard cytotoxic combinations in metastatic CRC. Several small molecule VEGF tyrosine kinase (e.g. cediranib, sunitinib, axitinib) are actually in phase 3 development in combination with standard combination cytotoxic regimens in metastatic CRC.

The anti-epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab are also active in metastatic CRC. The activity has been shown initially in chemotherapy refractory metastatic CRC. The combination of cetuximab with irinotecan is more active in this setting than cetuximab alone. The activity of anti-EGFR antibodies is confined to patients with a KRAS wild type tumour. Recent data showed also an increased PFS of cetuximab in combination with chemotherapy in less advanced stages of metastatic CRC. The PFS of the combination FOLFIRI/ cetuximab was significant longer than that of FOLFIRI alone in a phase 3 trial in the first line treatment of CRC and of cetuximab/irinotecan compared to irinotecan alone in the second line treatment of metastatic CRC. It has recently been shown that the activity of the anti-EGFR antibodies is confined to patients with a KRAS wild type tumor and it is known that +/- 60 % of patients with colorectal cancer have a KRAS wild type tumor.

Many open questions and challenges remain in relation to the use of the anti-VEGF and anti-EGFR antibodies in metastatic CRC. Answers are needed to optimize the outcome for patients and the more optimal use of the resources. A crucial challenge is to demonstrate which patients are more likely to respond to bevacizumab-containing regimens and to the anti-EGFR antibodies cetuximab and panitumumab. The mentioned data on KRAS as a predictor for activity are very important and are certainly the beginning of a new era of in the management of CRC. They help us to predict which patients will not benefit from cetuximab and panitumumab. Further research is needed to determine which markers will help us to predict the activity of cetuximab and panitumumab on top of the KRAS status and also to find predictive markers for angiogenesis inhibitors.
A second important challenge is the strategic question on the best combination, on the best sequence and on the most optimal use of the different cytotoxic agents in combination with the biologicals in CRC. Amongst other relevant clinical questions are questions on the optimal duration of bevacizumab, on the continuation of bevacizumab after progression, on the significance of skin rash in patients treated with anti-EGFR antibodies and on the real impact of bevacizumab and cetuximab in the neoadjuvant preoperative treatment of liver metastases. An important challenge is the understanding of the mechanism why tumours that initially respond to a combination of cytotoxics and biologicals may become resistant to this combination.

In conclusion: the management of patients with advanced colorectal cancer has improved. The introduction of the classic cytotoxic agents, as well of the targeted agents contributed to the progress. The angiogenesis inhibitor, bevacizumab, as well as the EGFR inhibitors have clearly increased the therapeutic armamentarium of patients with metastatic colorectal cancer. The introduction of the new agents offer also prospects for an increased chance of a longer survival for patients with metastatic colorectal cancer. The major challenge is now to implement strategies in which patients can be selected, based on molecular characteristics and/or pharmacogenomic profiles so that the new drugs and the resources can be used optimally for our patients with metastatic colorectal cancer.
Adenoid Cystic Carcinoma of the Cervix: Case Report and Review of the Literature

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Introduction

Adenoid cystic carcinoma is a malignant epithelial neoplasm derived from the salivary glands. Primary adenoid cystic carcinoma of the cervix is extremely rare, accounting for less than 1% of all cervical carcinomas. We report a case of primary adenoid cystic carcinoma and a review of the related literature.

Case presentation

A 68 year-old woman was admitted with signs and symptoms suggestive of a cervical cancer. The radiological and pathological investigations confirmed the diagnostic of primary adenoid cystic carcinoma of the cervix at Stage IIIB according to the International Federation of Gynaecology and Obstetrics classification. The patient was managed successfully by concurrent chemo-radiotherapy.

Conclusion

The optimal management of adenoid cystic carcinoma cannot be established for certain. From our case and from the literature, it appears that combined treatment (surgery, radiotherapy, and chemotherapy) is necessary for achieving a long-term remission. Concurrent chemo-radiotherapy appears to be a logical option for locally advanced disease.
The Use of Trastuzumab in Adjuvant or Metastatic Breast Cancer in Three Medical Oncology Centers in Algeria

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Background

Trastuzumab was introduced as a standard of care, three weekly for 18 cycles post chemotherapy for patients with breast cancer over-expressed Her2/neu+. Cardiac function was monitored every 3 months.

Methods

Patients were eligible if they had breast cancer over-expressed Her2/neu+. All patients had PS ≤ 2, adequate organ function, a baseline LVEF > 55% measured before therapy and all patients had an echo/cardiology assessment before, an adjuvant treatment with Trastuzumab or following chemotherapy. In Algeria, Her2/neu is over-expressed in breast cancer in 25% of cases, tested by IHC.

Results

From June 2006 to March 2008, 182 patients were enrolled in the study because of Her2/neu+ and received Trastuzumab in that time period with 24 (13.2%) of patients receiving it in the metastatic, 158 (86.8%) in the adjuvant settings. In Centre Pierre & Marie Curie, we enrolled 152 patients, from Medical Oncology of Constantine, we had 16 patients and from the Oncology-Hematology Center of Annaba, we enrolled 14 patients.

The median age was 43 years old (24-70) and 47% were hormone receptor positive. Most of patients received an anthracycline or taxane containing regimen. 7 (3.8%) patients had to stop treatment by Trastuzumab because of cardio toxicity. 5 patients were unable to tolerate Trastuzumab and to follow the treatment. All other patients, in the adjuvant setting, had a normal or sub-normal cardiac function. There was a significant increase in metastatic breast cancer-death if Trastuzumab started > 12 weeks after chemotherapy, which has implications for practice and introducing Trastuzumab earlier in the care of the patient.

Conclusion

The review shows a good conformity to practice guidelines, a safety use of Trastuzumab which must be associated to the determination and the follow-up of the cardiac function, a baseline LVEF before, in and after the treatment. The efficiency of the use of Trastuzumab is incontestable, with a prohibitive cost, but for the safety of patients.
Everolimus (Afinitor®, RAD001): Current and Future Development Across Multiple Indications

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Everolimus is a rapamycin derivative that acts as a signal transduction inhibitor. Its target is mTOR (mammalian target of rapamycin), a key serine-threonine kinase regulating protein synthesis and ultimately cell growth, cell proliferation, angiogenesis, and survival. Downstream of PI3/AKT, mTOR can be considered as a component in the PI3K/AKT/mTOR pathway known to be dysregulated in numerous human cancers.

Everolimus has been in development across a variety of tumor types in areas of significant unmet medical need since 2002, both as monotherapy and in combination. Two administration schedules have been thoroughly assessed: intermittent (70 mg weekly) and daily (10 mg) – the latter providing continuous inhibition of mTOR. Accumulating preclinical and clinical evidence suggests that continued mTOR inhibition is associated with a higher degree of efficacy.

Everolimus is currently under regulatory assessment for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of VEGFR-TKI therapy (sunitinib and/or sorafenib). Median progression-free survival of 4.9 months and 1.9 months were reported for everolimus and placebo, respectively (HR 0.33, p<0.001). Efficacy results were consistent across subgroups (age, gender, prior therapy, race, … etc). Most common adverse reactions were stomatitis, rash, fatigue, and diarrhea.

Safety and efficacy data from a large number of phase-I/II trials have led to the development of several pivotal phase-III registration studies. This broad development program reflects indications (both oncology and non-malignancies) where everolimus may convey potential benefit in areas of high unmet medical need. Updated safety and efficacy data will be presented.

### Everolimus (Afinitor®, RAD001): placebo-controlled phase III clinical development program

<table>
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<th>Indication</th>
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<td>Pancreatic islet cell tumors</td>
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<td>Tuberosis sclerotic complex</td>
<td>Growing subependymal giant cell astrocytomas (SEGAs) N=69, 2:1 randomization Large kidney angiomylipoma (≥ 3 cm) N=69, 2:1 randomization</td>
<td>ORR, TTP, seizure control, surgical intervention, cognitive function ORR, TTP, seizure control, surgical intervention, cognitive function</td>
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<td>Lymphoma</td>
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<td><strong>10 mg daily combination therapy</strong></td>
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<tr>
<td>Carcinoid tumor</td>
<td>Progressing secretory tumors N=428</td>
<td>PFS, ORR, duration of response, OS Sandostatin LAR® Depot ± everolimus</td>
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<td>Breast, Her2/neu +</td>
<td>1^st line, no prior therapy for advanced disease N=717, 2:1 randomization</td>
<td>PFS, OS, ORR, CBR Paclitaxel (80 mg/m²) d1, 8, 15-pq w + weekly trastuzumab ± everolimus</td>
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<td></td>
<td>Trastuzumab-resistant, ≤ 3 prior chemotherapy regimens for advanced disease, prior taxane treatment N=572</td>
<td>PFS, OS, ORR, CBR Weekly vinorelbine (25 mg) + weekly trastuzumab ± everolimus ± everolimus</td>
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<td>Breast, ER+</td>
<td>Refractory to letrozole or anastrozole N=705, 2:1 randomization</td>
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<td>OS, TTP</td>
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CBR: Clinical benefit rate; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression
Translation and Validation of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) Version 4 Quality of Life Instrument into Arabic Among Lymphoma Patients who Underwent High Dose Chemotherapy and Autologous Stem Cell Transplant

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Objective

To translate into Arabic and validate the “Functional Assessment of Cancer Therapy –Bone Marrow Transplant” (FACT-BMT) quality of life questionnaire, among patients who underwent high dose chemotherapy and autologous stem cell transplant (HDC-ASCT) for non Hodgkin’s lymphoma and Hodgkin’s lymphoma.

Methods

The Arabic translation followed the standard Functional Assessment of Chronic Illness Therapy (FACIT) translation methodology. Provisional Arabic FACT-BMT was pre-tested by personal interview of 20 native Arabic speaking patients. This version was then applied to the next 60 patients through telephonic (39) or personal (21) interview for validation. One lymphoma and autologous stem cell transplant expert (S. Akhtar) also developed 17 additional culturally adapted questions (Cultural Adapted FACT-BMT) for relevant cultural issues.

Preliminary result

Eighty patients, males 52 (65%), females 28 (35%) participated in the study. Of these, 76 were Saudis, 3 Yemenis and 1 Palestinian. At the time of study, median age was 32 years (15-62 years) and ECOG performance status was 0 in 76% and 1 in 19%. First 20 patients interviewed in pre-testing phase. All patients understood the questions well and no modification has to be undertaken.

The pre-test results indicated good content coverage and overall comprehensibility. All patients easily understood all items of Arabic version of FACT-BMT and high internal consistency in pre-testing phase is expected. Patients have high scores in all domains of quality of life including physical, social, emotional and functional well-being, indicating that most patients were leading a normal life.

Patients scored > 70% for not at all or a little bit only for nausea, trouble meeting needs of the family, having pain or feeling ill. Sixty-nine percent answered not at all or little bit for having lack of energy. Support from family and friends were > 80%. Quite a bit and very much satisfaction with sex life was 54%. Feeling sad was not at all or a little bit in 77%. Eighteen percent patients were concerned about their ability to have children; this is a reflection of younger patients being transplanted and also the social set up where the average family size usually exceeds 5 children. Statistical analysis is underway.

Conclusion

These data validates the first Arabic version FACT-BMT. This is likely to help large number of Arabic speaking patients, not only in the Middle East and Arab countries, but also in Europe and North America. Most of our patients enjoyed a good quality of life post HDC-ASCT.
Leiomyosarcoma of the Uterine Cervix: A Case Report and Review of the Literature

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Introduction

Leiomyosarcoma arising from the uterine cervix is an exceedingly rare tumor with only few cases reported in the literature. We report an observation about this disease.

Case report

A 41-year-old female presented with complaints of worsening monorrhagia of 6 months duration. Pelvic examination revealed a large tumor of the uterine cervix extending into the upper vagina. Pelvic MRI confirmed the presence of a cervical uterine tumor. The cervical biopsy with immunohistological study concludes leiomyosarcoma (grade II). Metastatic workup revealed the presence of pulmonary metastasis. The treatment consisted of chemotherapy based on ifosfamide and doxorubicin. The evolution was marked by a clinical and radiological progress.

Discussion

Cervical leiomyosarcomas tend to occur in the premenopausal period. The most common symptom is abnormal vaginal bleeding. Because the number of reported cases in the literature is so small, the optimum means of managing cervical leiomyosarcoma has yet to be established. It seems appropriate that when faced with this disease process, the clinician therefore looks to the current accepted standards for the management of uterine leiomyosarcoma for guidance. Several factors have consistently been found to demonstrate value as prognostic indicators predictive of outcome in patients diagnosed with uterine LMS. Most notable among these are tumor stage, grade, and mitotic count.

Conclusion

In summary, because there is so little experience with leiomyosarcoma in the uterine cervix, its ultimate prognosis is unclear. Thus, more cases of this unusual morphologic variant and longer follow-up of existing and future cases are needed to determine the clinical behaviour of this neoplasm.
Hepatitis C Infection and Non Hodgkin Lymphoma in 44 Egyptian Patients: A Single Institute Experience

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Background

Hepatitis C virus (HCV) infection has recently been recognized as a potential cause of developing B-cell lymphoproliferative disorders. Several studies have reported a significantly higher prevalence of HCV in patients with NHL (i.e. 20% in Italy, 6.4% in other European countries, 14% in Japan and 11% in USA). HCV is endemic in EGYPT, according to the WHO (article: HCV in Egypt, by Z.Mesban & A.Wakil; 2003), HCV has been declared a global health problem with approximately 3% of the world’s population infected with HCV- Egypt is considered to contain the highest prevalence of HCV in the world, the national prevalence rate of HCV antibodies positivity was estimated by the Egyptian ministry of health & population (MOHP) in 1999 to be 18.9%, with genotype 4 representing over 90% of the cases in Egypt.

Aim

Defining the epidemiological aspect of HCV infection in newly diagnosed untreated NHL Egyptian patients with special emphasis on the relationship between HCV infection & B cell-NHL, raising the possibility of combining antiviral therapy (Interferon/ribavirin) with lymphoma treatment protocols in HCV+ve NHL patients to achieve better therapeutic outcomes.

Patients and Methods

Sera collected from patients recently diagnosed with NHL presented to our institute from December 2008 through March 2009. Forty four patients were included in our study; 29(65.9%) Males and 15(34.1%) Females with a mean age of 42 (range 18-65). Patients were screened for the presence of HCV antibodies with commercially available serological tests. Reverse transcription-PCR was carried out in 9 cases for quantitation of HCV-RNA.

Results

Thirty one patients (70.5%) were high grade NHL and 13(29.5%) low grade NHL. HCV positive patients were 16(36.4%) and 28(63.3%) were HCV negative.

Quantitative RT-PCR was performed for 9 HCV positive patients out of 16 and they were all in the low to moderate viraemia range (1x10⁴ -5x10⁵ IU/ml).

Conclusions

In our study inspite of the limited number of patient’s results suggest the presence of a correlation between HCV & NHL, but we are still screening patients coming to our institute to establish a statistically significant correlation.
Demography of Plasma Cell Dyscrasias in Egypt

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Background

Plasma cell dyscrasias (PCD) are a group of diseases characterized by the proliferation of a plasma cell clone which produces a monoclonal protein (M-protein). The most common type is Multiple Myeloma (MM) followed by Waldenstrom’s macroglobulinaemia (WM) and Light chain disease (LCD). Hypocalcaemia, anemia, renal damage, increased susceptibility to bacterial & fungal infections, and impaired production of normal Immunoglobulins as well as diffuse osteoporosis are common clinical manifestations of MM (Grethlein S, medicine; MM; 2004). Thus, plasma cell dyscrasias present in different fields of clinical practice, making it of great interest to study the epidemiology of this disease.

Aim

In the present study, we described the epidemiological aspect of PCD presenting to our oncology unit of Cairo university hospitals during seven years period of time.

Patients and Methods

We retrospectively reviewed the medical records of 204 patients diagnosed with MM, WM and LCD in our unit from January 2002 through March 2009. One Hundred and Twenty Five out of 204 are Males and 67 are Females, with a mean age 45 years (range 28-70).

Results

The study included 204 newly diagnosed and untreated PCD patients, 182 were affected by MM (89.2%), 9 by LCD (4.4%) and 13 by WM (6.4%). IgG myeloma was diagnosed in 133 (73.1%) patients, IgA myeloma in 49 (26.9%). K light chain in urine was found in 139 (68.1%) patients and λ in 65 (31.9%). The International Staging System (ISS) using B2 micro globulin and albumin as staging parameters was applied to classify 115 patients out of 204; accordingly 41 patients were found to be in stage I, 71 in stage II and 3 in stage III.

Conclusion

This descriptive study enabled us to identify the pattern of distribution of different PCD referred to our unit, drawing our attention to the increased incidence in females & to the younger age at presentation (down to 28 and 32 years old). Further collaborative studies in association with other institutions will help establish the Egyptian configuration of PCD needed for prospective individualization of therapeutic guidelines.
A Descriptive Study of Flow Cytometric Analysis of 159 Acute Leukemia Patients: A Single Institute Experience in Egypt

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Background

This study was carried out to analyze the proportion of acute myeloid leukemia (AML), acute lymphoblastic leukemia (T / Pro and Pre B-ALL), biphenotypic lineage and Undifferentiated acute leukaemia among 159 acute leukemia (AL) patients. We also analyzed the coexpression of AML with lymphoid cell surface markers (T / B) and ALL with myeloid cell surface markers. By this method more than 98% of acute leukemia cases can now be precisely allocated to their respective lineages (Channa J et al. 2000).

Aim

To determine the proportions of each lineage and the coexpression of myeloid and lymphoid cell surface markers for later detection of their prognostic impact.

Patients and Methods

Data of 159 consecutive cases of AL were analyzed in our study from Jan 2005 through March 2009. Thirty four were Children (12 AML; 12 B-ALL; 8 T-ALL and 2 biphenotypic), 125 adults (79 AML; 27 B-ALL; 16 T-ALL; 1 biphenotypic and 2 undifferentiated). Ninety one patients were males and 68 were females. Flow cytometry was performed for all AL cases using the standard protocols. Myeloid associated markers included (MPO, CD 13, CD33, CD117, CD15, CD14 and CD64); T-lymphoid associated markers (Tdt, CD2, CD3, CD5 and CD7); B-lymphoid associated markers (Tdt, CD10, CD19, CD20 and CD22); Lineages non specific markers (CD34, HLADR) and Panleucocytic marker (CD45). Fluorescence labeled antibodies were obtained from (Becton Dickinson, U.S.A) and run on FACSCALIBER using CELLQUEST software.

Results

Ninety one patients were AML, 63 were ALL, 3 biphenotypic and 2 undifferentiated AL. Six (6.6%) out of 91 AML patients showed CD19 coexpression; 7(7.7 %) with CD7, 3(3.3%) with CD15. Three (4.7%) out of 63 ALL patients with CD 13 coexpression and 3(4.7%) with CD 33 coexpression.

Conclusion

Flow cytometry enabled us to determine the proportions of each lineage of acute leukaemia as well as the coexpression of cell surface markers between different lineages. Follow up of the prognostic impact of this coexpression on our patients is still in progress.
False Positive $^{18}$FDG PET/CT Findings in a Cohort of 1800 Patients Treated for Malignant Lymphoma

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Background/Purpose

$^{18}$FDG PET/CT has been emerging as an invaluable tool in the management of patients with lymphoma; particularly by providing accurate staging, restaging and assessment of response to therapy. However, FDG is not a specific tracer, it has an inherent limitation by localizing to non-tumorous tissues/non malignant tissues including post therapy induced inflammation.

Materials and Methods

2010 consecutive PET-CT scans were performed in eighteen hundreds patients with HD and DLBCL patients in the period of October 2005 to December 2008. FDG-PET-CT was performed to evaluate the response to therapy post either chemotherapy or chemoradiotherapy. The average time post therapy is 4-6 weeks. Whole body PET-CT was performed approximately 60 minutes post injection of 10-15 mCi of 18F-FDG using an 8 slice PET/CT system (Discovery LS;GE) and utilizing low Kvp (100kVp),with 80 mA, Slice thickness of 3.75 mm, and Pitch of 1.675:1.

The criteria for response assessment set up by the subcommittee of International Harmonization Project in Lymphoma (JCO, 25: 571-578,February 2007) has been adopted in interpreting all the cases.

Results

Thirty one patients (31/1800, 0.02%) had an abnormal FDG uptake that was falsely reported as positive for residual disease.

The standard of reference for PET/CT findings was the histopathology in 20 patients and radiological/clinical follow up for at least 6 months in 11 patients.

Reactive, and lymphoid follicular hyperplasia represented the majority of the histopathological findings (18/31, 58%). Granulomatous disease was seen in 2 patients.

Furthermore, infectious process including, pneumonia, upper respiratory tract infection, gastritis and prostatitis were seen in (11/31, 35%).

Conclusion

Standardized approaches for performing and interpreting PET/CT scans have minimized significantly the false positive rate.

Owing to the non specificity of FDG, the majority of the false positive findings were related to either therapy induced inflammatory process or infectious process.
Whole Body $^{18}$FDG-PET Predicts Progression Free and Overall Survival in Patients with Squamous Cell Carcinoma of the Esophagus: A Prospective Trial

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Purpose

A previously published study suggested that measured of therapy induced changes in tumor glucose metabolism by positron emission tomography (PET) with the glucose analog $^{18}$Florodeoxyglucose ($^{18}$FDG) predicts the response, survival and recurrence in adenocarcinoma of esophagogastric junction. The aim of this study was to prospectively validate these findings in squamous cell carcinoma (SCC) of the esophagus.

Patients and Methods

Twenty one patients with squamous cell carcinoma of the esophagus who were potentially resectable were included in the study. All patients underwent $^{18}$FDG-PET imaging before 1st cycle of neo-adjuvant chemotherapy and 14 days at least after the 3rd cycle. Patients were classified as metabolic responder when the metabolic activity of the primary tumor had decreased by 50% or more at the time of second $^{18}$FDG-PET.

Results

The median age of the study cohort was 60 (+/- 9.7) years, 12 patients were males and 9 were females. $^{18}$FDG-PET demonstrated increase activity in the primary tumor in all patients. Metabolic response was shown in 14 patients (66%), while 7 patients didn’t show metabolic response. Metabolic responders showed a high clinical response rate (92 %), median progression free survival (PFS) (16.4 months) and median overall survival (OS) (35.3 months). In contrast, prognosis was poor for metabolic non-responders with clinical response rate of 42% (p=0.025), median PFS of 7.13 months (p=0.032) and median OS of 12 months (p=0.038).

Conclusion

Current results demonstrate that changes in tumor metabolic activity after neo-adjuvant chemotherapy predicts PFS and OS in esophageal SCC patients. These data provide the basis of clinical trials in which early assessment with $^{18}$FDG-PET could change the pre-operative treatment guided by the metabolic response.
Vascular Endothelial Growth Factor (VEGF-C) Signaling through FLT-4 (VEGFR-3) Mediates Leukemic Cell Proliferation and Survival

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Key words: VEGF-C, FLT-4, KDR, Leukemia.

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Similar to solid tumors, growth of leukemia may also be angiogenesis dependent. Tyrosine kinase receptors specific to endothelial cells are expressed on certain subsets of leukemias.

In response to leukemia-derived pro-angiogenic cytokines, endothelial cells release increasing amounts of the vascular endothelial growth factor (VEGF) family member, VEGF-C. In turn, signalling of VEGF-C through the receptor tyrosine kinases VEGFR-3 (FLT-4) and VEGFR-2 (KDR) promotes leukemia survival and proliferation. VEGF-C induces receptor phosphorylation, leukemia proliferation and increased survival, as determined by increased Bcl-2/Bax ratios.

This study included 30 newly diagnosed patients with leukemia: 20 ALL and 10 AML cases as well as 10 matched controls. Patients and control group were tested for the expression of VEGF-C, VEGFR-3 (FLT-4) and VEGFR-2 (KDR) gene using RT-PCR.

Among ALL patients (20 cases), VEGF-C, FLT-4 and KDR were expressed in 65%, 70% and 30% of cases respectively. Among AML patients (10 cases), VEGF-C, FLT-4 and KDR were expressed in 60%, 70% and 40% of cases respectively. Among ALL and AML cases (30 cases), 44.4% and 33.3% respectively showed associated expression of VEGF-C and FLT-4. While, 11.1% of ALL and none of AML cases showed associated expression of VEGF-C and KDR. Finally, 44.4% of ALL and 66.7% of AML cases showed associated expression of FLT-4 and KDR.

Ten patients were followed up, six ALL and four AML cases. Of the followed ALL cases (6 cases), 3/6 were in remission and were VEGF-C -ve (two were FLT-4 +ve and one was KDR +ve), 2/6 were resistant to treatment and were VEGF-C +ve and FLT-4 +ve (one was KDR+ve), while the remaining patient (1/6) died during induction and was VEGCF +ve, FLT-4+ve and KDR +ve. Of the followed AML cases (4 cases), 3/4 were in remission (one was VEGF +ve and 2 were FLT-4 +ve), while the remaining patient (1/4) was resistant to treatment and was VEGF-C, FLT-4 and KDR +ve. The number of either ALL and AML patients expressing both VEGF-C and FLT-4 was higher than those expressing both VEGF-C and KDR. This could lead to the assumption that VEGF-C acting through FLT-4 may play a more significant role than acting through KDR in the pathophysiology of acute leukemia.

These results may identify VEGF-C/FLT-4 pathway as novel therapeutic target for the treatment of leukemias.
Visual Inspection with Acetic Acid (VIA): Is it the Hope for Prevention of Cancer Cervix in Egypt?

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Background

In Egypt, cervical cancer is the 2nd most common cancer in women after breast cancer. Cervical cytology is presently considered to be the only test known to reduce cervical cancer incidence in organized screening programs in developed countries. However, an organized screening program is difficult to implement in developing countries where resources are scarce. Visual inspection with acetic acid (VIA), as an alternative to cervical cytology, is of particular interest to developing countries because it is inexpensive, only requires supplies usually locally obtainable, and can be competently performed by non-physicians with proper training.

Objective

To evaluate VIA as a feasible screening program in our locality. To explain our experience regarding this simple screening method in Egypt.

Methods

1550 patient of various complaints were subjected to cytological examination of the cervix, examination of the cervix by VIA (visual screening with 5% acetic acid), Colposcopic examination and biopsy under colposcopic guidance for histopathological examination.

Results

On cytological examination; 1240 cases with no CIN, 177 cases with CIN1 (LSIL) and 100 cases with CIN2-3 (HSIL). On (VIA) we found about 199 VIA positive cases and 1351 VIA negative cases. With Histopathology which is the final diagnosis and is our reference diagnosis our result is: 57 cases are LSIL and 70 cases are HSIL. The sensitivity of cytological examination is 58.13% and its specificity is 93.7% with positive and negative predictive values 60.97 and 91.6 respectively.

Conclusion

In resource restricted countries like Egypt, VIA may find a place as a low technology and low cost method of screening for cancer cervix.
Primary Cerebral Lymphoma: About 16 Cases

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Introduction

Primary cerebral lymphoma (PCL) represents 1% of non-Hodgkin’s lymphomas and 3% of all brain tumors. The immunosuppression is a favoring factor clearly established but the origin of this phenomenon in the immunocompetent population is still mysterious.

Objectives

Identify epidemiological, clinical, histological and radiological characteristics of this pathology.

Materials and Methods

We reviewed all cases of PCL collected at the National Institute of Oncology during the period between 2004 and 2007.

Results

We had reviewed 16 patients, 13 men and 3 women. Their average age is 44 years with extremes ranging from 16 to 63 years. The average delay of consultation was 6 months with extremes ranging from 1 to 24 months. The first reason for consultation was the occurrence of headache and rebel focal deficits. The HIV came back negative in 4 patients and was not performed in the remaining patients. All patients underwent a CT scan and/or magnetic resonance imaging MRI brain (10 patients with CT + MRI) for the diagnosis of brain tumor whose nature. Histology was studied by means of stereotactic biopsy. Histologically, as it was reported in the literature, lymphoma diffuse large B-cell represents the majority of LCP (eg 11 patients). Lymphoma small B cells was found in 2 patients and 2 patients had a T-type lymphoma.
Cervical Synovialosarcoma: Case Report and Review of the Literature

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Introduction

Sarcomas of the head and neck region are a rare and diverse group of neoplasms and only account for less than 1% of all neoplasms that occur in this area. Herein we describe a case of neck synovial sarcoma.

Case presentation

A 32-year-old girl with no significant past medical history, presented with a 6-month history of cervical mass. Physical examination revealed a right cervical mass (8cm).

Initial TDM revealed a right cervical mass.

The patient underwent near total tumor resection; encapsulated 7 cm _ 4, 5 cm_ 3 cm mass was resected. Histopathological examination showed a hypercellular tumoral tissue with monophasic pattern. Immunohistochemical study revealed cytokeratin and EMA positively in the epithelial component and diffuse PS100 positivity.

External beam radiation therapy was performed using 6 MV X-rays from a linear accelerator, with daily fraction of 2 Gy, 5 fractions per week and a total dose of 70 Gy was delivered. The spinal cord was excluded from the radiation fields after 40Gy.

Discussion

Synovial sarcomas of the head and neck region are extremely rare, accounting for only less than 10% of all head and neck soft tissue sarcomas. This soft tissue neoplasm generally does not originate from synovial tissue and probably originates from the pluripotent mesenchymal cells. About 100 cases of the synovial sarcoma of the head and neck region have been reported in the international literature. Microscopically, the classic form of the synovial sarcoma has biphasic pattern composed of two cell population: epithelial cells and spindle cells. Special immunohistochemical stains and cytogenetic studies can help in confirming the diagnosis.

Standard local therapy for Synovial sarcoma follows the general principles of soft tissue sarcoma treatment with wide surgical resection and adjuvant radiotherapy when appropriate, with or without adjuvant chemotherapy. Combined modality therapy of this aggressive tumor yields better results; however, the 5-year survival rate of these patients is poor and ranges from 25% to 55%. Local or distant failure is seen in the approximately 80% of cases. Lung is the most common site of metastases.

The size of primary tumor, histological grade, age, sex, adequacy of surgery, status of surgical margins, and radiation dose are prognostic indicators.

Conclusion

Synovial sarcoma of the head and neck is extremely rare. Standard local therapy is surgical resection and adjuvant radiotherapy when appropriate, with or without adjuvant chemotherapy. The prognosis is poor.
Colorectal Carcinoma at Al-gamhouria Teaching Hospital, Aden, Yemen

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Abstract

An analysis of 50 cases colorectal cancer in predominantly a disease of the old and less than 1% of patients are below 20 years in most reports.

Aim of study

This study aims to retrospectively analyze the pattern of patients with colorectal cancer seen in Oncology Unit, at Al-Gamhouria Teaching Hospital from January to December 2006.

Materials and Methods

All cases of colorectal cancer presented to Al-Amal unit, Al-Gamhouria Teaching Hospital in Aden Yemen between January and December 2008 were reviewed and the data was analyzed to determine age, gender, residency, clinical presentation, histological types and staging of disease and treatment.

Results

A total of 50 cases were included in the study, 34 (68%) male and 16 (34%) were female. (M:F 2.1:1). The mean age at presentation was 48.8 years for females and 56.4 for males. Abdominal pain (70%) and bleeding per rectum (50%) were the main presenting complaints. The most common site are rectum (34%), ascending colon (22%) and sigmoid in 18% of cases. 82% of tumors of colorectal region were adenocarcinomas, the majority of which (66%) were well to moderately differentiated adenocarcinoma. 70% of the cases diagnosed in late stages.

Conclusion

There is increase incidence of colorectal carcinoma. Bad outcome directly related to late detection of cancer and >70 % of cases in stages III and IV
Radiation Therapy in Elderly Patients

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Cancer is a disease that predominantly occurs in older patients. Radiotherapy is one of the most powerful treatment against cancer. To define an adapted strategy and to offer a better quality of life to the elderly constitute the challenges of the oncology of this beginning of century.

Objective

The purpose of this study is to report clinical aspects, patients and tumor’s characteristics, radiation therapy methods and treatment results of elderly patients.

Patients and methods

Retrospective analysis carried on 100 patients aged to 75 years or more and treated by irradiation in National Institute of Rabat in 2006.

Results

underway

Conclusion

Radiation therapy is a major therapeutic weapon in the treatment of the cancer. The elderly patients have to benefit from it. A geriatric evaluation and an adaptation of its modalities remain necessary and the integration of oncogeriatrician in the multidisciplinary decision is indispensable.
Small Cell Neuroendocrine Carcinoma of the Uterine Cervix

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Small cell neuroendocrine carcinoma (SCNEC) of the uterine cervix is a rare finding representing 2%–5% of all cervical malignancies. The natural history of this disease differs from the more commonly seen squamous cell or adenocarcinoma of the cervix. Patients diagnosed with SCNEC are more likely to have lymph node metastases and lymphovascular space invasion, and their clinical course is frequently marked by local and distant failure.

Objective

We intend to expose through four cases of SCNEC of the cervix the peculiar therapeutic and prognostic aspects of this type of cervix tumours.

Materials

Case 1: A 42 years old patient diagnosed with a stage IIIB tumour of the uterine cervix. The morphological and immunohistochemical study retained the diagnosis of SCNEC. A radiologic examination revealed no metastasis. The patient received a radiotherapy (46 Gy) associated with Etoposide and Cisplatin based concomitant chemotherapy followed by brachytherapy (24 Gy). 7 months later, we discovered an adenocarcinoma of the pancreas as well as hepatic and adrenal glands metastases. She received a palliative chemotherapy (Gemcitabine) and died 5 months later.

Case 2: A 40-year-old woman was admitted for an uterine cervix tumour stage IIIB. Based on morphological and immunohistochemical findings, the histologic diagnosis was consistent with SCNEC. The therapeutic approach was based on the concomitant radio chemotherapy. She died 5 months after the end of the treatment.

Case 3: A case of SCNEC stage IV of uterine cervix diagnosed at a 75-year-old patient. She reported a history of post menopausal metrorrhagia and haemoptysis during the 4 last months. A radiological examination revealed a lung and hepatic metastases. The patient received one cycle of Etoposide and Cisplatin based palliative chemotherapy and died 1 month later.

Conclusion

The cervical location of SCNEC is rare. Despite aggressive locoregional treatment with surgery and/or radiation therapy, relapse is common and adjuvant systemic chemotherapy is generally recommended. However, most patients develop metastatic disease and the prognosis is poor.
Primitive Neuroectodermal Tumor of the Breast: About 2 Cases


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Introduction

Neuroendocrine (NE) breast cancers encompass a heterogeneous group of tumours showing morphological features similar to those of NE neoplasms of the gut and lung and expressing one or more neuroendocrine markers (neuron specific enolase, chromogranins synaptophysin) in at least 50% of tumour cells. They are rare lesions representing about 2–3% of all breast cancers. The coexistence of both exocrine and neuroendocrine differentiation can lead to some uncertainty about the choice of the best antineoplastic strategy.

Case1: A 59-year-old woman was admitted to hospital with a tumor on her right breast. Mammography and ultrasonography reported a lesion measuring 3 cm. CT scan of the chest and abdomen found no abnormalities. Histopathological examination of the specimen obtained from a biopsy of the lesion detected an invasive breast ductal carcinoma. The patient underwent right mamectomy with axillary lymph node dissection. The final histopathologic diagnosis was primitive neuroectodermal tumor with 1N+/20N. Immunohistochemical detected synaptophysin(+), and cytokeratin(+), chromograninA(-) ,and PR(+) ER(-),Her2/neu (score1+). Adjuvant treatment consisted of chemotherapy, and radiotherapy to the chest wall. And additional hormonotherapy. The patient was followed-up every 3 months. Two years after treatment no recurrence was detected.

Case2: A 37 year old woman presented with a tumor in her right breast. Mammography and ultrasonography reported a lesion measuring 3 cm. Needle aspiration biopsy detected carcinoma cells. No distant metastasis was detected on various investigations such as chest XRay,liver ultrasound,bone scan and CT chest. The patient underwent tumorectomy with axillary lymph node dissection. The final histopathologic diagnosis was primitive neuroectodermal tumor with 20N-/20N. Immunohistochemical detected cytokeratin(-), chromograninA(+), NSE(+) and PR (-) ER (-). Her2/neu (-). Adjuvant treatment consisted of chemotherapy, and radiotherapy. Two years after treatment no recurrence was detected.

Discussion

Neuroendocrine tumors in the breast are rare, accounting for less than 0.1% of all breast cancers and less than 1% of all neuroendocrine tumors. Neuroendocrine carcinomas of the breast occurred mainly in older women around the end of the seventh decade of life. The clinical and radiological features of neuroendocrine tumors are non-specific, and fine-needle aspiration or core-needle biopsy examination is necessary for the diagnosis. The morphological features of the neuroendocrine carcinomas of the breast should be confirmed by immunohistochemical means or by electron microscopy. Immunohistochemically, NSE was used to study argyrophilic breast carcinoma, and it has been found to be positive in 16–50% of unselected breast tumors, even in the absence of argyrophilia or dense core granules. All these findings discouraged us from using NSE to define a breast carcinoma as neuroendocrine differentiated. In contrast to NSE, chromogranin and synaptophysin have been widely accepted as specific markers of neuroendocrine differentiation. Neuroendocrine tumor in the breast may represent either metastatic or primary lesions. The ductal carcinoma in situ component is the only absolute proof of the primary nature of the breast carcinoma. It is important to differentiate primary breast neuroendocrine tumor from metastatic disease to the breast because of differences in treatment.

Treatment, which may include surgery, radiotherapy, and chemotherapy, is based on clinical stage and the presence of metastases. Prognosis is variable and is dependent on the initial stage of disease.

Conclusion

Primary neuroendocrine carcinoma of the breast is rare—only about 30 cases have been reported in literature and it is important that these be recognized as a separate entity from the more common breast carcinoma keeping in mind the difference in behavior of the two tumors for planning therapy.
Chronic Hemangiopericytoma Involving the Retrorectal Space: Case Report


National institute of oncology, Morocco

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Introduction

Primary hemangiopericytoma (HP) of bone is rare, accounting for 0.1% of malignant primary bone tumors. Only a few cases of osseous hemangiopericytoma in the sacrum and involving the rectorectal space have been reported. We present such a case which was treated by surgical abdominal approach and radiotherapy.

Case report

A 42 years old woman suffered from low-back pain with radiation to the right leg and foot for two years. Physical examination revealed abnormal S1-S2 dermatome sensation. Digital rectal examination revealed a retrorectal mass. CT of the pelvis showed an osteolytic lesion of the S1 and S2 right sacral ala and its extension into the retrorectal space. Magnetic resonance imaging of the pelvis showed a large sacral tumor with prominent mass. Abdominal approach resection was indicated after surgical staff. Pathologic exams revealed a hyper cellular spindle-cell tumor into a high vascular pattern. At immunohistochemistry the tumor is CD 34 positive, and negative for actine smooth muscle and C-kit. It was finally recognised to be a hemangiopericytoma. Post operative MRI contol shows a residual sacral cavity communication with a retrorectal collection. Adjuvant radiotherapy has been indicated at about 45grays. Five month later she feels well.

Discussion

HP can arise in any part of the body owing to its vascular origin, but most frequently occurs in soft tissue. The ages of patients range from 12 to 90 years. Radiographic features are non specific, including osteolytic bone and cortical destruction with soft tissue extension. On histology HP cells typically cluster around numerous capillaries and usually contain round to oval nuclei. Immunohistochemistry (CD34) is helpful in the differentiation against other typical malignancies. Wide surgical excision is the treatment of choice for HP. Radiotherapy may couvert a non resectable lesion into a resectable one; the role of chemotherapy is still unclear. HP is capable of both local reccurence and distant metastasis but has low disease associated mortality.

Conclusion

At present day it’s the first case of HP involving the retrorectal space treated by local excision. Adjuvant radiotherapy is therefore useful in HP. The value of chemotherapy is still doubtful.
Ck 19 as a Predictor for Micrometastasis in Breast Cancer: Study Done on Non-Metastatic Egyptian Female Breast Cancer Patients

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Background
The standard method to detect disseminated epithelial cells (DEC) in bone marrow (BM) is immunocytochemistry (ICC). Several studies demonstrated that the presence of ICC stained cytokeratin 19 (CK19) positive cells in BM is associated with a poor prognosis (Diel et al., 1996; 2000; Singletary et al., 2002; Wiedswang et al., 2003). The value of this cytological method is limited by its low sensitivity, and is highly dependent on experience of the observer. Since the introduction of molecular based techniques, more sensitive quantitative methods have been developed based on polymerase chain reaction (PCR) methodology. The most commonly used molecular method for the detection of DEC relies on the screening for tumour associated and/or organ specific mRNA expression in cancer cells and on the absence of these gene products in the cells of the host tissue such as BM. The identification of an appropriate target gene is one of the most critical steps in the reverse transcriptase (RT) PCR approach to quantify DEC. Cytokeratins are widely evaluated as targets for the detection of DEC, and can be used for the prognostic/predictive evaluation of DEC.

Aim
To assess the efficacy of CK 19 as indicator for micrometastasis or predictor for relapse in non-metastatic breast cancer patients.

Patients and methods
CK 19 has been estimated in breast cancer patients using both ICC on BM biopsy compared to quantitative real-time PCR (QR-PCR) using Taqman fluorescent probes on ABI prism 7700 instrument (Applied Biosystems). Bone marrow samples were taken from 13 non-metastatic breast cancer female patients with average age of 52.5 yrs (40-65y) and 4 controls matching in age and sex. For exact quantification of gene expression (CK 19), an endogenous reference (housekeeping gene GAPDH) was used to correct for differences in the amount of total RNA added to the reaction, for compensation of different RT efficiencies and for compensation of PCR inhibitors in the sample. We used two different calculation methods to quantify our results; the ΔΔCt method and standard curve using 4 serial dilutions of Raji RNA extracted from a human B cell lymphoma line. Our results were compared to those of ICC using CK-19 antibodies (Ventana no.760-4281 /automated system) on BM biopsy specimens.

Results
CK 19 mRNA could be quantified by QT-PCR in all 4 control samples, with a mean ratio of 0.35 (considered as cutoff value) using standard curve method. Validation of ΔΔCt method was done and proved to be comparable with standard curve results. Eleven out of 13 patients proved to be positive above cutoff value. Two patients (15.3%) had very low CK 19 expression with values below cutoff. Using ICC these 2 patients had borderline results; and with further follow-up clinically no bone or organ metastasis was detected. Another 3 patients (23.1%) out of the 11 were proved to be positive by ICC (intensity of positivity was low) while having high expression of CK19 by PCR. Two of these 3 patients had metastasis in the form of liver deposits.

Conclusion
Estimation of CK 19 by molecular method (QT-PCR) proved to be superior to ICC in the prediction of possible relapse or metastasis in female breast cancer. Further studies with larger number of patients could clarify the prognostic significance of CK 19 in non-metastatic breast cancer patients. Inspite of limited number of patients in our study, we do recommend to add CK19 QR-PCR to the laboratory tests battery for female breast cancer.
Bronchial Carcinoid: Ten Years Experience

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Key words: Bronchial, Carcinoid, Experience, ten, years.

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Background

Broncho-pulmonary carcinoid is a low grade malignant tumor. These tumors are reported to represent 10% of all carcinoid tumors and 1-6% of all lung tumors. Eighty to 90% of tumors develop within a bronchus of subsegmental size or greater, while 10-15% arise in a mainstem bronchus.

This work was conducted to study bronchial carcinoid tumor regarding age and sex distribution, incidence rate, surgical techniques and patients’ survival.

Patients and Methods

Between 1998-2008, 31 patients with broncho-pulmonary carcinoid were included. Evaluation of the patients included, full history taking, full clinical examination, C.T scan of the chest and upper abdomen and fiber optic bronchoscopy. Pulmonary function tests were ordered for all patients. Bronchoscopic biopsy was obtained in 21 patients, transthoracic needle biopsy in 5 and the diagnosis was reached postoperatively in the remaining 3 patients.

Results

Among the studied patients, there were 13 males and 16 females, the mean age was 33 years. All male patients were smokers and none of female patients ever smoked.

Twenty five patients were symptomatic, the tumor was discovered accidentally in the remaining 6 patients. Bronchial carcinoid represented 22.4% of all carcinoid tumors and 8.2% of lung cancer patients referred to our institution during this period. Carcinoid syndrome was found in only one of our studied patients.

Operative procedures performed were: lobectomy in 8 (5 Lt. and 3 Rt.), bilobectomy in 2, pneumonectomy in 3 (2 Rt. And 1 Lt.) and 18 sleeve resections (sleeve lobectomy in 15, sleeve Rt pneumonectomy in 2 and one with bronchial resection and re anastomosis).

Postoperative pathology revealed 29 patients with typical and 2 with atypical carcinoid. The mean tumor size was 2 X 3.5 cm with a range of 1.5 X 1.8 cm – 3 X 4.5 cm.

Postoperative TNM staging was: 12 patients with stage IA (T1 N0), 15 IB (T2 N0), 2 IIA (T1 N1, T3N0), 2 IIIA (T2 N2).

Morbidity was encountered in 11 patients, in the form of arrhythmia in 5, pneumonia in 3 and prolonged air leak in 3 patient with no operative related mortality. Follow up data were available for 27 patients as 4 patients were lost to follow up. One patient with atypical carcinoid died 8 months postoperative from disseminated disease, the remaining 26 patients are alive disease free. Follow up duration ranged from 7-97 months. Overall survival rate was 81.5%.

Conclusion

Bronchial carcinoid is of low malignant potential with excellent survival following complete resection. Bronchoscopy should be done for all patients preferably by the operating surgeon.

Great effort should be carried out to resect this special type of lung tumor as surgery is considered the only line of treatment, due to low malignant potential, bronchoplastic procedures should be encouraged whenever indicated.
The Experience of the National Institute of Oncology in Nasopharyngeal Carcinoma

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The epithelial malignant tumours of the nasopharynx constitute an epidemiological, clinical and biological entity, different from other cervico-facial cancers. In our institute. It is the most common head and neck cancer.

Materials and Methods

A total of 188 patients with nasopharyngeal carcinoma were recruited in our institution between January and December 2006. The aim of this study is to expose the epidemiological, clinical and evolutional characteristics of this pathology.

Results

The median of age of the patients was 47 years (12- 77 years). 66% of the patients were male. The median time of consultation was 7 months. 80% of the patients presented cervical lymph nodes at the first consultation. The pathology exam had shown a UCNT in 90% of the cases. A CT scan of the nasopharynx was made among all patients. After a distant work up, the patients were classified according to TNM 2002 classification: 5% T1, 43.5% T2, 22.5% T3 and 24.5% T4. 12.5% of the patients had metastatic disease. Regarding treatment, 129 patients received neoadjuvant chemotherapy. The radiotherapy was delivered in 118 cases. 37 patients had no treatment. In 75% of the cases, the protocol of chemotherapy was based on anthracyclines / Platine. The median number of cures was 3. The chemotherapy was followed by a loco regional radiotherapy in 92% of the cases.

The evaluation of the treated patients assembled that 60% of the patients were in complete response, 8% in partial response. The evolution was marked by 10 cases of nasopharyngeal and/or nodal recurrences, 13 cases of distant metastases. The median follow up was 12 month. 47% of the patients are always followed in good control of their disease.

Conclusion

The progress of radiotherapy and the association of neoadjuvant and/or concomitant chemotherapy allowed an improvement of the local control and survival of patients suffering from nasopharyngeal carcinoma.
Rituximab Based Regimen May Decrease the Incidence of CNS Relapse in Patients with Diffuse Large B-Cell Lymphoma

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Keywords: Central nervous system relapse, diffuse large B cell lymphoma, RCHOP.

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Background

Relapse in the central nervous system (CNS) following initial treatment of diffuse large B-cell lymphoma (DLBCL) is an uncommon but fatal complication. However, the addition of rituximab improves the clinical outcome dramatically in DLBCL patients; its influence on CNS relapse is unproven.

Aim

This single centre retrospective study was conducted to investigate the incidence of CNS relapse, and to evaluate the impact of adding rituximab to standard CHOP (RCHOP) regimen without CNS prophylaxis in patients at risk of CNS relapse.

Patients and Methods

All patients with DLBCL diagnosed from April 2002 to December 2007 at sunnybrook cancer center were retrospectively identified in the Cancer Database. Patients were included if they were >16 years old, had advanced stage (stage III/IV, or stage I/II with B symptoms, elevated LDH or bulky disease, were treated with RCHOP regimen with curative intent and were free of CNS involvement at diagnosis. CNS relapse was diagnosed by CSF cytology, radiology or clinically.

Results

A total of 155 patients were newly diagnosed with DLBCL and treated with RCHOP only. 22 pts were excluded, 20 had CNS prophylaxis and 2 pts had CNS involvement. 133 pts were eligible (69 male and 64 female) Median age was 64 (Age≤60 was 59.4%). Stage III/IV was 69.9%. LDH was elevated in 59.4%. Bone marrow (BM) involvement and Extra nodal 2 were 18.05% and 25.6% respectively. EN sites were: (liver 4.5%, Bone 6.8%, Pulmonary 4.5%, kidney 3.01%, cardiac 1.5%, intestine 2.3%, testicular 1.5%). The International Prognostic Index was high-intermediate/high in 55.6%. Pathologically transformed was 12.03% were transformed from indolent histologies. BCL2 was positive in 65.4%, BCL6 was 48.9%, CD10 was positive in 49.6%, Ki-67 was >80% in 25%. All patients received RCHOP (Median 6 cycles, (range 2-8). Overall response (ORR) was 88.6%, CR/CRU 72.7% with a median follow up 24.6 months (range 2.6-75.5). 28 patients (21.05%) relapsed systemically. Two patients (1.5%) had a CNS relapse 1 brain parenchyma and 1 leptomeningeal one month after systemic relapse. The median time to CNS relapse was 10.4 mos (6.24-14.5 mos). In univariate risk factor analysis (LDH (p=0.8), IPi>3 (p=0.9), No of EN (p=0.9). Actuarial 5 y Overall Survival (OS) was 67.3% (95% CI 57-77%) and progression free Survival (PFS) was 65.7% (95% CI 52.3-78.6%).

Conclusion

Our data suggest that the addition of rituximab may reduce the risk of CNS relapse for poor risk patients likely through systemic control. Future prospective studies of rituximab-containing chemotherapies with CNS prophylaxis are warranted.
Genetic Profiling Signature of Multi-Drug Resistance in Breast Cancer

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Success in Breast cancer chemotherapy is challenged by development of tumors having a multi-drug resistance (MDR) phenotype. It is one of the major causes of failure to cancer chemotherapy. MDR is a multi-factorial problem, where several mechanisms are acting in concert with each other. The current study aims to evaluate differential expression profiles of some genes mediating MDR in resistant breast cancer cells. Genetic profiling signature of resistant MCF-7/Dox cells treated with doxorubicin (Dox) and chemo-sensitized with 2-methoxyestradiol (2ME, a natural estrogen metabolite) was identified using RT Profiler PCR Array. Out of 84 genes examined, 47 genes were found to have changes in gene expression in different treatment groups. Based on significance of results, four genes were chosen as representatives of the genetic events mediating development of MDR phenomenon. MDR1, Bcl2, P53 and Cyclin D1 genes were selected for complete evaluation because of their role in drug efflux systems, apoptotic signaling and cell cycle regulation. 2ME significantly increased sensitivity of the resistant MCF-7/Dox cells to cytotoxic effect of Dox by 2.9-folds. 2ME chemosensitizes resistant breast cancer cells by significantly down regulating expression of Bcl2 and Cyclin D1 genes by 2 and 3-folds respectively, confirmed by western blotting. Combination of 2ME to Dox increased caspase activity by 27 folds and arrested cell cycle in G1 and S phases compared to Dox alone. In conclusion, our results suggest that down regulation of expression of Bcl2 and Cyclin D1 genes, augmented caspase 3 activity and cell cycle block may account for chemosensitizing resistant breast cancer cells by 2ME.
Factors Predicting Brain Metastases in Adjuvant Breast Cancer Patients

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Keywords: Breast cancer; Brain metastasis; Prognostic factors.

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Background and Aim

The brain is increasingly being recognized as a sanctuary site for metastatic tumor cells in high risk breast cancer patients. Symptomatic brain metastasis develop in 10%-20% of patients with metastatic breast cancer, most often following disease progression at other sites, carrying a poor 1- and 2-year survival rates of only 20% and <2%, respectively. The objective of this retrospective analysis is to investigate the factors predictive of brain metastasis in adjuvant breast cancer patients.

Patients and Methods

We retrospectively analyzed breast cancer patients who presented to our center in the period from 2000 till 2006. Correlations were made between brain free survival (BFS) and different factors including age, menopausal status, hormone receptor status (ER & PR), Her-2/neu status, pathological grade, pathological type, tumor size and nodal status. BFS was computed using the Cox Proportional Hazards Model.

Results

Our study included 1732 patients of which 73 developed brain metastasis. The 5-year BFS was 84.5% for ER-ve, 86.4% for PR-ve, 84.2% for Her-2/neu +ve patients compared to 93.5% for ER +ve (p<0.001), 93.7% for PR +ve (0.006) and 92.5% for Her-2/neu -ve (0.002) patients respectively. Patients with grade III tumors had a shorter 5-year BFS of 81.2% compared to 93.1% for those with grade I-II disease (p<0.001). Positive lymph nodes had a marginal significance of a shorter BFS as well (90.2% vs. 94.5%; p=0.042). There was no significant difference seen according to age, pathological type or menopausal status. In a multivariate analysis model, histological grade and negative PR were the most significance.

Conclusion

Based on this analysis, patients with poorly differentiated tumors appear to have a higher probability of developing brain metastases as well as those with negative PR status. We could not draw solid conclusions regarding the predictive value of Her-2/neu gene being missing in a large number of the examined subjects. These patients could be good candidates for trials investigating the role of any prophylactic intervention to decrease their risk to develop brain metastases.
Serum Vascular Endothelial Growth Factor in Non-Small Cell Lung Cancer

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Background and Aim

Vascular endothelial growth factor (VEGF) is a potent angiogenic peptide expressed in a wide variety of tumors, and it stimulates angiogenesis and increases vascular permeability. Active angiogenesis of the tumor is a major contributor to the high metastatic potential of NSCLC.

Materials and Methods

In the period between Jun 2007 and Aug 2008, levels of VEGF were determined by ELISA in serum of 50 patients with NSCLC presented to medical oncology department, NCI, Cairo. In addition ten age and sex matched normal subjects were used as a control group. Correlation between VEGF at the time of sample withdrawal and different clinico-pathological parameters (Gender, Age, Performance Status, Pathological subtype, Stage of the disease, Platelet counts) and progression free survival of patients was done.

Results

The median value of serum VEGF 667.50 pg/ml. A significant difference between the values of VEGF in patients and healthy controls (p<0.001) was confirmed with a best statistical cut-off of 100 pg/ml (sensitivity = 94 %, specificity = 100 %). There was no statistically significant difference in the clinicopathological parameters including age, gender, histological type, stage, performance status and platelet count of the patients with NSCLC and VEGF. Patients with higher levels of VEGF had a lower median progression free survival compared to those with lower levels, yet this difference did not reach statistical significance (5 months vs. 7 months respectively; p=0.2).

Conclusion

The results of this study showed that serum VEGF levels were higher in NSCLC patients. However, it failed to correlate with different clinicopathological parameters which may attributable to small sample size. Further research is still needed for the complete understanding of the exact role of VEGF in NSCLC.
Male Breast Cancer in Tripoli/ Libya

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Background
Male breast cancer is very rare disease with an incidence of around 0.5%- 1%of the incidence of total breast cancer. Studies reveal an increase or stable incidence for male breast cancer over the last decades which are different compared with situation for female describing a constantly increasing incidence over the year. Male breast cancer is more frequently seen in family with mutation of BRCA1 gene but occasionally mutation is seen in BRCA1.

Objective
To study the epidemiology of breast cancer in male patients

Materials and Methods
1568 patients were registered in the period between Jan 1990 till June 2008, 22 patients were as male (1.4%) in Tripoli medical center.

Results
1.4% of patients were male with a mean age of 61 years. They tend to have advanced local disease as 65% of them are T3+T4 and 93.3% have positive lymph nodes. The preferred surgical treatment was mastectomy and axillary clearance in 65%. 85% are invasive duct carcinoma. Regarding hormone receptor status, 70% are estrogen and progesterone positive. 71% received chemotherapy as Anthracycline based. During follow up the overall recurrence rate was 47%.

Most common site of relapse was bone in 37.5%. Overall survival rate at 1st, 2nd, and 5th are 82.4%, 64.3%, and 57% respectively. Two patients were brothers, both of them presented at same times as stage IV disease, one died after 9 months with liver and lung and bone metastases. The other one lived with bone metastases from Dec2003, till Jan 2008, where presented with multiple lytic lesions negative bone scan and high immunoglobulin infiltration of bone marrow by plasma cell and was diagnosed as multiple myeloma.

Conclusion
In comparison to female patients with breast cancer, male patients are older and they have more advanced disease and have more hormone positive disease.
Survival of Breast Cancer Women < 35 Years Treated in Tripoli/Libya

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Study Objective

To study survival of breast cancer in very young age women < 35 years over the 2000-2005.
To relate recurrence rate and survival to risk factors as lymph node involvement, and Estrogen and progesterone status.

Design and Setting

Non-randomized retrospective study in patients with breast cancer confirmed by biopsy in Oncology department in Tripoli medical center.

Patients

Five hundred fifty two patients were seen, 93 patients less than 35 years representing 16.8% were included in this study in the period between January 2000, and December 2005.

Results

Patients below 35 years of age represent 16.8% of our total patients. Their stages were not different from older patients. stage I (1.1% vs. 3.2 %), stage II (38.7% vs. 44 %), stage III (37.8%vs32.6%), and stage IV were (11.8% vs. 10.2%) (P= > 0.05).
Also no difference in tumor grade.

In the majority of the patients under 35 years estrogen and progesterone receptor status were negative (55.6%), but the majority of the patients over 35 years were estrogen and progesterone receptor positive (55.5%) (p=0.035).

Visceral metastases were more common in the under 35 years (50%) versus (29%) in patients above 35 years (p=0.04).

Overall recurrence rate at 1,2and 5 years and survival rate was better in node negative patients than node positive patients regardless of age (p=0.01).

Overall recurrence rate at 1,2and 5 years and survival rate was better in estrogen positive patients than in estrogen negative patients p=0.04.

Conclusion

Women less than thirty five have a poor prognosis despite a similar stage and grade to older women. These women have more estrogen and progesterone negative status tumors (p=0.035) and have greater tendency to develop visceral metastases than older women.
Survival of Breast Cancer Patients with Brain Metastases

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Study Objective

-To study survival of breast cancer patients with brain metastases.
-to study predictive value of tumor size, lymph node involvement and hormone receptor status on the occurrence of brain metastases and survival of patients with breast cancer

Materials and Methods

805 patients were diagnosed with breast cancer between Jan.2000 till June 2008 and registered in Oncology Department in Tripoli Medical Center.
44(5.5%) patients were included in this study that developed brain metastases diagnosed by CAT scan or brain MRI.

Results

Mean age of these patients was 43.6 years. 72.7% were premenopausal. These patients had large tumor size on diagnosis T3+T4 76.6%.
81.5% were node positive. 70.4% were stage III and IV.
37.5% had isolated brain metastases on presentation. 72.7% has negative hormone receptor status. 86.4 % (38/44) had recurrence at median duration of 16.5 months.
Of these 68.4% had brain metastases out of them 53.8% had only brain metastases and 46% had brain and soft tissue or bone metastases.
31.8 % presented as second relapse, all with brain metastases .in 71.4% as isolated brain metastases and 14.3% with brain and soft tissue as liver and lung. All patients received cranial radiotherapy. 6/26(23%) of these patients received Cisplatin based chemotherapy. 4/6(66.7 %) of them are alive.
Median duration of survival from first recurrence was 5.8 months. Median duration of follow up was 24.5 months. 11/44 are alive.

Conclusion

Patients with brain metastases are mostly premenopausal and have large tumor size, have more node positive disease and negative estrogen receptor status (p=0.001). Their median duration of survival was poor at only 5.8 months.
Actual or Adjusted: Which Should We Use?

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Background

Calculation of chemotherapeutic drugs doses was standardized to Body Surface Area, with the aim to produce optimum systemic drug level & minimize drug toxicity; it also can be very challenging in obese cancer patients. Obesity is a common & increasing problem affecting the developed world, beside it’s considered an endemic problem between the Egyptian populations. It represents a condition of excessive adipose tissue with its currently accepted definition based on Body Mass Index (calculated as follows: Weight (kg)/ [Height (cm) 2]) obesity is defined as Body Mass Index >30 kg/m2); it once believed that obese patients who received chemotherapy on their actual body weight would result in increased toxicity, secondary to distribution of lipid soluble drugs into the adipose tissue.

The current practice of using Body Surface Area in dosing anti-cancer drugs was implemented in clinical oncology half a century ago, by using Adjusted Body Weight it’s assumed that cancer patients would receive a dose of a particular cytotoxic drug associated with an acceptable degree of toxicity without reducing its therapeutic effect2, it also has been proposed as a method to improve the accuracy of calculating chemotherapeutic drugs doses especially for obese patients.

Aim

Considering the use of adjusted body weight for calculation of chemotherapeutic drugs doses and its impact on the disease free survival in obese female breast cancer patients.

Method

Significant correlation between a given demographic characteristic(body surface area and disease free survival). The dose of chemotherapeutic drugs based on Body Weight, and the traditional formula is DuBoin and DuBoin formula which is the most widely accepted nomogram which is simplified by Mosteller to:

$$\text{BSA (m2)} = \sqrt{\text{Ht. (cm)} \times \text{Wt. (kg)}/36003.6}$$

Adjusted Body Weight= Ideal Body weight+ 0.4 (Actual Body Weight- Ideal Body Weight)

Ideal Body Weight for females = 45 + 2.3kg for each inch > 60 inches*, *60 inches =152 cm

We compared two groups of Adjuvant female breast cancer patients, both groups received FEC 100 regimen ( Epirubicin 100mg/m2, 5-FU 500 mg/m2, Cyclophosphamide 500 mg/m2) 5for (4-6 cycles), between the period (2000-2008).

- Group A: (149 patients) received their regimen based on their actual body weight.
- Group B: (100 patients) received their regimen based on their adjusted body weight.

Conclusion and Recommendations

At median follow up period of 17 months there was statistical significance of disease free survival in favor of group B (patients received their regimen according to the adjusted body weight), (70.3 months Vs. 52.4 months, p= 0.004). Both groups were homogenous in other factors: ER, PR, HER2 status, Age, T & N, which by comparison showed non-significant difference. Using adjusted body weight is considered a proper alternative method for the calculation of anti-cancer drugs doses. An effort is currently using the substantial information to retrospectively examine outcome with respect to toxicities.

References

5. Nutritional Considerations in the intense care unit by Scott A.Shikoras American society for parental & internal nutrition, Robert P330.
6. DuBoin D, DuBoin EFA Formula to estimate the approximate surface area in height & weight is known. -Arch inter Med 1916; 17:863-871
Molecular Biology of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the fifth most frequent tumor and the third cause of tumor-related death in the world, and is now a major health problem worldwide. In the United States, the incidence increased by 80% between 1975 and 1998, whereas the incidence of all other malignancies declined. Based on mathematical models, its frequency has been estimated likely to further increase in the upcoming years because of the spread of the hepatitis C virus, and the longer survival of patients with liver cirrhosis.

In fact, in Western European as well as North American countries, HCC usually develops in cirrhotic patients, and cirrhosis is the most important risk factor. So far, therapy has been mainly ablative, including embolization, alcohol or acid instillation, radiofrequency ablation and radical surgery, and although some improvements prognosis and survival are still unsatisfactory, even for those patients undergoing liver transplantation. On the other hand, we cannot rule out the possibility that an advanced stage of the underlying liver cirrhosis can be the cause of death in patients with HCC. Tumor recurrence, together with metastasis formation, represents the most common reasons for the unfavorable prognosis, and no therapies are currently available to block or reduce tumor growth and/or metastasis dissemination. This is mainly because the molecular and biologic mechanisms regulating cancer growth and spread are still poorly understood. For instance, the underlying chronic liver disease, as well as the pathologic characteristics of the tumor, does not explain why the natural history of HCC is so different in each patient. In fact, growing evidence suggests that intrinsic biologic characteristics of the tumor in terms of proliferation, survival, and invasiveness are probably due to different composition and activity of the microenvironment, this leading to very different clinical outcome. For example, only a few of the questions that are still seeking an answer includes why and how HCC develops and can recur, why it develops metastases, why the sites of metastasis are so different, and how the malignant phenotype changes, often becoming very aggressive and invasive during the natural history. In this review I will try to point out what we know and what we need to know to be better able to face the challenges posed by HCC. Moreover, I will deal with the capacity of invasion and spread of HCC in the liver or in other organs, devoting a particular interest to the interactions between the surrounding microenvironment and the cancer cells.

The tissue microenvironment is a kind of biologic “soup” made up of different cell types (hepatic satellite cells, Kupfer cells, macrophages, endothelial cells); extracellular matrix (ECM) proteins such as laminins (Las), collagens, fibronectin, vitronectin, fibrinogen; proteolytic enzymes: matrix metalloproteases (MMPs), serin proteases; growth factors: transforming growth factor (TGF)-b1, hepatocyte growth factor etc. To invade, HCC cells need to penetrate through the tissues, negotiating this progression with the ECM proteins. However, this does not happen as a result of a breakdown of the molecular tissue boundaries but rather due to the unlocking of a dynamic gate. Proteolytic enzymes such as MMPs and serin proteases act as molecular scissors, that can cleave different components including ECM molecules, growth factors etc. changing their biologic properties, with a consequent effect on the HCC malignant Phenotype.

In fact, in the last few years, the “seed and soil” theory of Paget formulated in 1889 has been revisited in light of the growing evidence suggesting that metastases occur as a consequence of modifications of the microenvironment (the soil), rather than of the “primary metastatic genes” we have focused on for many unsuccessful years.

Metastatic dissemination or multifocal tumor?

The possibility that more than one nodule may be detected in patients with HCC has been known since 1957, when this was pointed out by Plopper and Schsffiner, but this manifestation has been most commonly considered as a multifocal carcinoma rather than a metastatic cancer, although such an assumption would be quite unusual for a malignant type of cancer like HCC. More recently, improvements in diagnostic techniques together with the availability of larger portions of tissue obtained from radical surgery or from liver transplantation, have made more systematic studies possible, thereby showing the presence of satellite micronodules around the main lesion, and so suggesting that HCC effectively is an invasive cancer. This is consistent with the recurrence of HCC in transplanted liver, which would otherwise be difficult to explain. The distinction between multifocal or metastatic nodules is not merely academic as the occurrence of metastasis is correlated with worst prognosis.

Among the different sites of metastasis, the liver represents the most frequent target, whereas the blood vessels are the most dramatic, being associated with a particularly unfavorable prognosis. “Metastatic dissemination or multifocal tumor?” is not a Hamletic question, because the 2 possibilities are not mutually exclusive as cirrhotic liver can generate more than one cancer nodule with the
same, still unknown mechanisms, during the history of the disease, as observed for other tumors, that is, urinary bladder. However, the identification of these 2 distinct hypothesis seems to be an underestimated problem by clinicians although a patient with a multifocal tumor has a better prognosis than a patient with a metastatic cancer. The main problem is still how to differentiate between the two, as the currently available morphologic criteria are definitely obsolete. Molecular genetic approaches seem to be the most appropriate to investigate the clonality of the different nodules: monoclonal multiple nodules stem from a common malignant precursor, as in metastatic lesions, whereas different clonalities are an expression of distinct tumors, as in multifocal HCC.

A more sophisticated approach to investigating a common pattern of chromosomal alterations has documented karyotypic alterations serving to differentiate between multifocal tumor and metastatic HCC. Similar results have been obtained by different investigators, showing that multiple HCC nodules are an expression of metastasis rather than of multifocal cancer in more than 60% of cases. However, in both studies, the techniques used could not be immediately introduced into clinical care, as it is not reasonable to perform multiple biopsies in patients to assess the correct diagnosis based on chromosomal or DNA alterations. These types of studies are very sophisticated and would need more clinical validation, also in view of the possibility that some alterations might not be the rule for HCC of multifocal origin. In conclusion, it is important to consider HCC as a highly metastatic cancer with a particular tropism for blood vessels, in which other tests are needed to recognize a metastatic from a multiple HCC.

Is HCC invasiveness a tumoral or a peritumoral problem?

In HCC tissue, the microenvironment seems to play a key role because the malignant cells grow embedded in a microenvironment enriched with ECM proteins, deposited as a consequence of the underlying cirrhosis. HCC cells, like other epithelial cells, cross talk with the surrounding ECM proteins thanks to several integrins, which act as transmembrane receptors. In the last few years, many proposed a model whereby α3β1 integrin, the main receptor for Ln-5, is present on the cellular surface of invasive but not of noninvasive HCC cells in vitro; consistently, α3β1 integrin was detected only in the tissue specimens obtained from aggressive and invasive HCC. Ln-5 is a member of the Lna family that has been reported to be involved in the metastatic spread of several malignancies after the proteolytic cleavage of its γ2 chain. In the liver, Ln-5 is expressed "de novo" in HCC but is absent in the peritumoral tissues; furthermore, the γ2 chain has been found to be expressed along the invasive edge, thus correlating with the occurrence of metastasis and with a worse survival and prognosis. Which cell type secretes Ln-5 in the liver is not yet known, but HCC cells that express α3β1 integrand can use Ln-5 as a preferential route to invade surrounding tissues, whereas HCC cells that do not express α3β1 do not migrate and do not invade. However, these cells can acquire migratory and invasive abilities through TGF-b1 that stimulates the expression of the integrand α3β1 at a translational level, on the cellular surface of the "noninvasive" HCC cells, that thus acquire migratory and invasive properties. TGF-b1 has been reported to be increased in the serum of HCC patients, stored in an inactive form in the microenvironment, where it can be activated after proteolytic cleavage by MMP-2 or MMP-9. Consistently, in HCC, a decreased expression of the tissue inhibitor of MMP-2, responsible for a proteolytic imbalance, has been reported.

This induces the activation of TGF-b1 and the metastasization of the HCC. Whether the proteolytic imbalance is brought about by the HCC cells or by other surrounding cells such as myoepithelial or inflammatory cells, as reported in breast and colon cancer, respectively, is not yet known. Another possibility is that inflammatory cells are commonly present in the tissue surrounding the cancer, and may represent an important source of proteolytic enzymes that can activate TGF-b1, inflammatory cytokines, growth factors, etc. This is the rationale behind the proposed use of anti-COX-2 as a potential anticancer drug. In any case, it is very difficult to define each component of the microenvironment, also because up to now studies have usually been focused on investigating the biologic functions of just one or few components present in the microenvironment. Several ongoing studies are investigating the "fingerprint" of HCC compared to the peritumoral tissues, using highly technologic approaches based on microarray techniques, proteomics, etc., and different hierarchical genes have been reported, but the interpretation of the results is strongly limited until the biologic role of those genes has been explained in an experimental model.

Molecular Mechanisms of HCC

An extensive study of HCC resulting from three of the main etiological factors HCV infection, HBV infection, and chronic alcohol intake indicates common molecular/genetic changes, with Rb1, p53, and Wnt the main pathways affected. Typically, tumors associated with alcoholism have more frequent alterations of Rb1 and p53 pathways than those caused by HCV infection. The most common alterations were p16INK4A methylation, loss of Rb1 expression through promoter methylation, and Cyclin D1 amplification. Analysis of HCC from human and animal models demonstrates up-regulation of the MAPK pathway as well as genes associated with an activated cell cycle. In addition the down-regulated genes mainly encode hepatocyte specific gene products and detoxification enzymes producing a less differentiated phenotype.

Later in hepatocarcinogenesis tumor cells undergo increasing levels of chromosomal aberrations including loss of gene heterozygosity. P16INK4A normally inhibits cyclin dependent kinases (cdk) 4 and 6 which block G1 phase progression via dephosphorylation of Rb, the latter of which binds to and inactivates E2F1. Germ line mutations of this tumor suppressor protein have been identified in adult cases of HCC in Switzerland suggesting familial HCC however, the concept of inheritable HCC is relatively new and requires further confirmation and analysis. Diethylnitrosamine-thioacetamide treatment of Fischer rats, which induces HCC, also causes hypermethylation of the p16INK4A exon 1 in the later stages of carcinogenesis, further highlighting its importance in this process. Mutations of β-Catenin are commonly observed in the early development of HCC and disruption of this Wnt signaling protein affects the expression of its target genes including c-myc, c-jun, cyclin D1 and β-bronectin β-Catenin is an important submembranous protein that functions in cell–cell adhesion. Its mutation disrupts normal cell–cell interactions and strongly stimulates hepatocellular growth. P53 is the most common molecular target in human carcinogenesis.

However, a study of primary HCCs from many different origins shows that frequency of mutation of this tumor suppressor was low. Usually mutations of p53 are recognized only in advanced stages of HCC and it is not a prerequisite for hepatocarcinogenesis.

The most common mutations of p53 in HCC are the G to T transversions in codon 249 caused by aflatoxin exposure. Recently, work to begin to define the complex signaling networks involved in the development of HCC has been undertaken using DNA–microarray-based gene expression profiling of stored human HCC.
Analyses of gene expression arrays have identified two distinct subtypes of HCC based upon relative gene expression patterns, termed subclass A and B. These two distinct subgroups carry dramatically different survival curves and patterns of gene expression. Subclass A that carries a poor prognosis has high levels of expression of genes associated with proliferation and ubiquitination. Expression of apoptotic proteins in subclass B HCC is low. Conversely, subclass B tumors express lower relative up-regulation of growth pathways and ubiquitination proteins but express high levels of antiapoptotic proteins. Subclass A cancers may involve a greater degree of c-myc dysregulation or that associated with transforming-growth factor alpha expression while providing little evidence of β-catenin expression. Conversely, subclass B HCC appears associated with variable expression of B-catenin and appear to have a larger expression of the transcription factor E2f1. Work is ongoing to further identify differences in patients with HCC. These differences may have profound effects in the future diagnosis as well as in choosing molecular pharmacologic targets to improve outcomes associated with chemotherapy.

Conclusions

In conclusion, what we know best is that our knowledge of HCC biology is definitely still poor. The importance of gaining a deep understanding of the biologic and molecular mechanisms of HCC growth and metastasis seems to be underestimated by clinicians.

Nevertheless, there is a strong demand for new therapies, although their development is hampered because the potential therapeutic target is still unclear. Furthermore, HCC is a cancer with peculiar characteristics, due to the underlying cirrhosis that could limit drug administration because of potential hepatotoxicity. In addition, the altered tissue remodelling commonly occurring in liver cirrhosis could trigger cancer aggressiveness because of activated signal pathways. As consequence of this impediment, and based on other cancer models, biologic therapy targeting microenvironment components seems to be a potentially interesting strategy. Pharmaceutical research in this sense would be greatly improved by a greater insight into the identification of the molecular mechanisms responsible for the different biologic and clinical behavior of HCC.
Cost Effectiveness in Cancer: A dream Will Come True

Kasr El-Eini Center of Clinical Oncology, Faculty of Medicine, Cairo University.

ISSN: 2070-254X

Introduction

Today’s cost-sensitive health care environment has created competitive and challenging workplace for clinicians and pharmacists. Competition for diminishing resources has necessitated that the appraisal of health care goods and services on the cost of health care[5]. A challenge for health care professional is to provide quality patient care with minimal resources. Paying for cancer treatment can be an issue in itself. This is especially true when cancer treatment continues for an extended time and involves chemotherapy[3]. Among cancer survivors younger than 65, one in five patients delay getting necessary cancer treatment or avoid it entirely just because of the cost, according to a 2006 study by the US centers for disease control and prevention[4].

Aim

Pharmacoeconomics evaluation of cost of chemotherapy drugs, considering the use of adjusted surface area instead of actual in calculation of the doses of anticancer drugs in order to:

- Maximize the number of patients treated.
- Maximize quality of treatment.
- Optimum Efficiency.
- Improve public & individual health.
- Achievement of Equity & Effectiveness.

Material and Method

The dose of chemotherapeutic drugs based on Body Weight, and the traditional formula of DuBoin and DuBoin which is the most widely accepted nomogram and simplified by Mosteller to: BSA (m2) =√Ht. (cm) * Wt. (kg)/36003.[1]

Adjusted Body Weight = Ideal Body weight+ 0.4 (Actual Body Weight- Ideal Body Weight)[1]

Ideal Body Weight for females = 45 + 2.3kg for each inch *60 inches =152 cm2. [1][2]

When applying these equations on an average female breast cancer patient received FEC 100 regimen (Epirubicin 100mg/m2, 5-FU 500 mg/m2, Cyclophosphamide 500 mg/m2) who weights 90 kg & her height is 160 cm:

- Her Actual Surface Area= 2m2, she will receive:
  - Epirubicin 200 mg
  - Cyclophosphamide 1000 mg
  - 5-FU 1000 mg

- The Adjusted Surface Area on the other hand will be: 1.75 m2, she will receive:
  - Epirubicin 175 mg
  - Cyclophosphamide 875 mg
  - 5-FU 875 mg

Result

A cycle of this regimen using the Actual Surface Area will cost 2530 Egyptian Pound and a course of 6 cycles will cost 15,180 Egyptian Pounds.

A cycle of this regimen using the Adjusted Surface Area will cost 2310 Egyptian Pound and a course of 6 cycles will cost 13,860 Egyptian Pounds.

A significant reduction in the cost of the chemotherapeutic course when using the Adjusted Surface Area by 1320 Egyptian Pounds, representing about 8.7% reduction.

Conclusion and Recommendation

Conducting a pharmacoeconomic research in public hospitals under supervision of ministry of health to provide a large scale research is required. By understanding the principles, methods, and applications of pharmacoeconomics, health care professionals will be prepared to make better, more-informed decisions regarding the use of pharmaceutical products and services.

References

1. DuBoin D, DuBoin EF. A formula to estimate the approximate surface area in height & weight is known - Arch inter Med 1916; 17:863-871
4. Basic clinical pharmacokinetics by Michael E.Winter.
Community Cancer Concerns, From a Population - Based Registry

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One of the main objectives of a population based cancer registry , is highlighting the community cancer concerns. Gharbiah Population-based Cancer Registry (GPCR), is the only and first – up till now – population based cancer registry in Egypt. It has been successfully functioning since Jan. 1999. The data of GPCR, is actively collected from 67 sources including some facilities outside Gharbiah that treat Gharbiah patients. Recently, GPCR data of 1999-2002 has been accepted for publication in the well known book «Cancer Incidence in Five Continents volume IX » issued by IARC-WHO. Forty eight African registry data sets were submitted to IARC-WHO , and only five were accepted. Compared to other accepted datasets , the population coverage of Gharbiah is the highest (4.2 million), and Gharbiah data is the most accurate.

Compared to other Arab countries , age standardized incidence rate (ASR) of male cancer , per 100 000 in Gharbiah (154), is higher than Tunisia (126), Algeria(98), Kuwait (121), Jordan(123) and Saudia(60), but lower than Qatar(180), and Bahrain (166).

As for female cancer, ASR per 100 000, in Gharbiah (137), is higher than Tunisia (95), Algeria(96), Kuwait (120), Jordan(127) and Saudia(61), but lower than Qatar(216), and Bahrain (159).

Breast cancer, ranks first amongst female cancers in Gharbiah-Egypt with ASR of 41.9/100 000, occupying the 27th percentile rank. This means that 73 % of registries worldwide has higher incidence of breast cancer than Egypt. This rate is close to that of South and Central America, but far below rates in Europe (64.2), Oceania (73.9) and North America(90.4). Our main concern, of breast cancer in Egypt is its rank on the top of female cancers as well as its late stage at presentation. In-situ and localized, lesions constitute only 25% of GPCR cases compared to 63% % in SEER series.

An interesting finding, is the low incidence of cancer of cervix uteri , compared to other countries , in the area. It has an ASR , of 2 /100 000. Based on this fact, we do not support the idea of a national vaccination program for prevention of cervical cancer. Our community cancer concerns , from a population based registry, should be the basis for planning a National Cancer Control Program.
Pentavalent Technetium-99m-dimercaptosuccinic Acid [99mTc(V)-dmSa] Brain Spect Versus Proton Magnetic Resonance Spectroscopy (1H-mrs) in Assessment of Glioma Recurrence Post Radiotherapy

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Nuclear Medicine department, NEMROCK center and radiology departments, Cairo University, Egypt

ISSN: 2070-254X

Introduction

The differentiation between recurrent tumor progression and radiation therapy effects in subject previously treated for glioma is problematic. Computed tomography and magnetic resonance imaging offer imperfect discrimination between viable tumor and post radiation necrosis/glisis. Both 99mTc(V)-DMSA brain SPECT and 1H-MRS may be useful for differentiate between tumor recurrence and radiation necrosis. The aim of this study was to compare 99mTc(V)-DMSA brain SPECT versus 1H-MRS for detection of viable glioma after radiation therapy.

Methods

Both exams were performed on 24 glioma patients, previously operated upon and treated with radiotherapy. SPECT images were acquired 3 hours post 740 MBq of 99mTc(V)-DMSA administration with a dual-head gamma camera. Tumor to normal (T/N) uptake ratio was calculated as: mean counts of tumor ROI (T) ÷ mean counts of mirror symmetric normal ROI (N). 1H-MRS was performed using a 1.5 T system equipped with a spectroscopy package. SPECT and 1H-MRS results were compared with pathology after new surgery or with follow-up.

Results

SPECT and 1H-MRS showed recurrence in 9 patients (confirmed by biopsy or follow up) and both were negative in 6 patients. SPECT and 1H-MRS disagreed in 9 cases of recurrence (7diagnosed as positive for viable tumor by brain SPECT& 2 by 1H-MRS). SPECT and 1H-MRS sensitivity in detecting recurrence as compared with surgical biopsy or follow up was 88.8% and 61.1% respectively with an accuracy of 91.6% & 45.8% respectively.

Conclusions

99mTc(V)-DMSA brain SPECT is more accurate in detecting and differentiating glioma recurrence from post radiation changes as compared to 1H-MRS.
The Lebanese Society of Medical Oncology held its seventh biannually conference (LSMO 7) at hotel Le Royal Dbaye, Lebanon, from 13 to 15 of November 2008. The Title of this national forum was “Commitment to Cure Cancer”.

Lebanese medical oncologists, radiotherapists, pathologists, oncologic nurses and cancer care givers were gathered along with hundred of arab physicians to attend this forum.

The opening ceremony took place in the evening of the 13th of November. The address of H.E. the minister of health Dr. M.J. Khalife focused on the role of ministry in organizing drug distribution and to cooperate with oncologists to reduce unjustified expenses. In his turn, Dr G. Aftimos, President of the Lebanese order of physicians, highlighted the role of research in the progress of cancer therapy and the harm caused by uncontrolled and non scientific therapies.

Dr Sami Khatib, general secretary of the Arab Medical Association Against Cancer (AMAAC) called in his address all arab associations to join their efforts to enrich our regional education and research. He invited the LSMO to be an active partner in the next AMAAC conference in May 2009 at Cairo.

The opening ceremony was preceded by pathology workshop conducted by Pr. Keith Kerr, expert in chest pathology, and followed by his special conference. He stressed on the expending role of molecular biology determination and of non small cell lung cancer sub classification in order to tailor the adequate chemotherapy. The presentation of Pr. Kerr was attended and appreciated by our colleague pathologists and pulmonologists.

Confirmed benefit of adjuvant chemotherapy and its crucial role in saving life was exposed by different presentations and speakers: Christophe Louvet in colo-rectal cancer and pancreas, Axel Le Cesne in soft tissue sarcoma, and Dominique Grunenwald in non small lung cancer. Moreover, Paul Ellis showed the benefit of new targeted therapy in the adjuvant setting of breast cancer.

New modalities of treatment of adult soft tissue sarcoma were presented by Axel Le Cesne, as well as advances in pediatric sarcomas by two experts in pediatric oncology : Marie-Dominique Tabone, and Christophe Bergeron.

2004 results of the National Cancer Registery were presented by Ali Shameseddin. Incident cancer case recorded was 7197, and age- standardized incidence rate was 179.3 per 100,000. The five most frequently diagnosed cancer sites in men were: lung (15.7%), bladder (15.6%), prostate (15.4%), colo-rectum (8.6%) and NHL (7.6%), while in women were: breast (38.2%), colo-rectum (7.8%),
NHL (5.9%), lung (5.9%) and ovary (4.6%).

Nurses’ conference was characterized by the huge number of attendees, and was chaired by Mrs Ursula Rizk, President of the Lebanese Order of Nurses, and by Rahif Jalloul, LSMO vice-president. Patient safety, manipulation safety, handling of new targeted therapy, and transfusion were the main topics of the conference, presented by Marwan Ghosn, Wael Abi Ghanem, Fadi Farhat, and Khaled Ibrahim respectively. Moreover, Ms Anne Frangie addressed in this conference objectives and achievements of “Faire Face Association” as NGO dedicated to cancer patients support, and Ms Nada Nassar treated the issue of stomatitis as serious side effect of cancer treated patients.

Three medical company sponsored symposia were displayed. Paul Ellis in Roche symposium, discussed the role of targeted therapy in advanced breast cancer, Chritophe louvet, in Sanofi-Aventis symposium, developed the state of the art approach of metastastic colo-rectal cancer, and Axel Le Cesne, in Novartis symposium, highlighted the success of targeted therapy in the treatment of gastro-intestinal stromal tumors (GIST).

Lebanese young investigators abstracts were presented and evaluated in two sessions: one for oncology fellows and the other for oncologic nurses. Awards sponsored by Pierre Fabre were delivered in a special session and went to the fellows: Celine Boutros for her study “Phase II trial of sequential Gemcitabine and carboplatin followed by Paclitaxel as first line treatment of advanced urothelial carcinoma” and she received the first price.

Second price was equally divided between Clement El Khoury and Philippe Aftimos for “Epidemiological study on invasive breast cancer surgically treated at Hotel-Dieu de France Hospital” and “Fludarabine + Cyclophosphamide and Fludarabine + Cyclophosphamide + Rituximab in the treatment of indolent NHL and CLL” respectively. Awards for nurses were divided equally between Yolla Greige for “Safety profile of biweekly schedule of liposomal doxorubicin (Caelyx) in salvage therapy of adult solid tumors” and Salma Faddoul for “Decision of palliative care in patients with advanced cancer”.

Like the previous ones, LSMO 7 achieved a remarkable success by the impressive number of national and arab attendees and by its outstanding scientific level. Closing remarks were delivered by LSMO president at the forum end, including invitation to all attendees to join the Best of ASCO in Beirut on July 2009.
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The Pan Arab Journal of Oncology (PAJO) is the official Journal of the Arab Medical Association Against Cancer (AMAAC). It is a quarterly publication targeting health professionals interested in the oncology field. It is a multidisciplinary peer-reviewed journal that publishes articles addressing medical oncology, malignant hematology, surgery, radiotherapy, pediatric oncology, geriatric oncology, basic research and the comprehensive management of patients with malignant diseases in addition to international oncology activities, congresses & news.

The journal will be addressed, as a first step, mainly to the professionals in the hematology & oncology field in the Middle East region and North Africa. The goal is to share local & regional research activities news and to be updated with international activities. We hope, with your support, to achieve our following objectives:

1. Promote and encourage research activities in the Arab World.
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4. Improve the level of scientific publications arising form the Arab World.
5. Keep health professionals connected and exposed to the activities of different Arab cancer societies.
6. Share with our immigrant compatriots their activities & feedback in this field.
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All reviews must be clinically oriented, ie, at least half the review must describe studies that detail human impact, marker effect on prognosis, or clinical trials. Review Articles should be prepared in accordance with the Journal’s Manuscript Preparation Guidelines, and will be reviewed in the same manner as Reports from Clinical Trials. Reviews are limited to 4,500 words of body text, excluding the abstract, references, figures, and tables. The editors also suggest a limit of 150 references.

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4. Manuscript Preparation Guidelines

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The first page of the manuscript must contain the following information: (1) title of the report, as succinct as possible; (2) author list of no more than 20 names (first name, last name); (3) names of the authors’ institutions and an indication of each author’s affiliation; (4) acknowledgments of research support; (5) name, address, telephone and fax numbers, and e-mail address of the corresponding author; (6) running head of no more than 80 characters (including spaces); (7) list of where and when the study has been presented in part elsewhere, if applicable; and (8) disclaimers, if any.

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Abstracts are limited to 250 words and must appear after the title page. Abstracts must be formatted according to the following headings: (1) Purpose, (2) Patients and methods (or materials and methods, similar heading), (3) Results, and (4) Conclusion. Authors may use design instead of Patients and methods in abstracts of Review Articles. Comments and Controversies, Editorials and Correspondence do not require abstracts.

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results and prognostic factors among 138 patients with advanced Hodgkin’s disease treated with the alternating MOPP/ABVD chemotherapy. Ann Oncol 5:S53-S57, 1994 (suppl 2)


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